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REMARKS

It is respectfully requested that the Examiner enter and consider the changes made in Claims 3 and 9 which are indicated in the Listing of Claims set forth in Appendix I attached to this paper.

Accordingly, applicants have revised the wording of the preamble of those claims to refer to --preventing or reducing the effects of aging processes or harmful environmental effects on human skin or human hair-- instead of *"protecting human skin or human hair against aging processes or harmful environmental effects"* and *"protecting"*, respectively. The alternative wording introduced into Claims 3 and 9 is based on applicants' disclosure on page 2, indicated lines 23 to 26[1] and indicated line 35 et seq.[2], in conjunction with page 1, indicated line 9, to page 2, indicated line 3, of the application[3]. No new matter has been added.

The Examiner has rejected Claims 3 to 9 and 11 under 35 U.S.C. §103(a) as being unpatentable in light of the teaching of ***Jiang et al.*** (**PNAS 97***(21), 11494-11499 (2000)*) when taken in view of the teaching of ***Burton et al.*** (**CA 103***:215586 (1985), which summarizes an article published in* **J. Am. Chem. Soc. 107**, *7053-7065 (1985)*[4]). In this context the Examiner applies the disclosure of ***Burton et al.*** for its showing that α-CEHC is known in the art as a compound having great antioxidant potential. It is, however, respectfully noted that the investigations of ***Burton et al.*** pertaining to the antioxidant effect of α-CEHC are investigations into the inhibition of the autoxidation of styrene[5]. ***Burton et al.*** also mention[6] that

> *[a] number of food preservation tests have shown that Ic is superior to α-T as an antioxidant. Since Ic is less reactive towards*

---

1) "... the object of the present invention was to provide ... the cosmetic effects already mentioned ..."

2) "... this object is achieved by the use of chroman derivative ..."

3) A corresponding disclosure is, for example, provided on page 4, indicated line 27, to page 5, indicated line 11, of the application.

4) A copy of ***Burton et al.***'s article is herewith enclosed for the Examiner's convenience.

5) Note, for example, Table I on page 7054 of ***J. Am. Chem. Soc. 107***.

6) Note the section relating to *"Inductive Effects"* on page 7060, left hand column, of ***J. Am. Chem. Soc. 107***.

peroxyl radicals than α-T in homogeneous nonpolar solvents (see Table I), its effectiveness in food preservation must have some other origin.

The disclosure of ***Burton et al.*** therefore corroborates that the antioxidant potential of a compound is unsuitable to suggest or imply that the compound will exhibit its antioxidant potential when it is applied in an environment which differs from the investigated environment. The antioxidant potential of a compound therefore cannot suggest or imply that a useful effect will result when the compound is applied to human skin or human hair. The foregoing is further corroborated when the data which are available from the teaching of ***Jiang et al.*** concerning the effects on epithelial cells and ***Burton et al.***'s data on the inhibition of the autoxidation of styrene (IAS) are reviewed together:

Compound	IC_{50} according to ***Jiang et al.***[a)]	10^4 k_1 value (IAS) according to ***Burton et al.***[b)]
γ-tocopherol	4 μM	140
γ-CEHC	30 μM	no data
α-tocopherol	no effect	320
α-CEHC	no data	370

a) First para, page 11494 of ***Jiang et al.***
b) Table I, page 7054, of ***Burton et al.***

The compilation shows that γ-tocopherol which has -with a k_1 value of 140×10^4- a lower antioxidant potential exhibits in the treatment of epithelial cells an IC_{50} of 4 μM, cf. a comparably high activity. In contrast thereto, α-tocopherol exhibits no effect on epithelial cells although α-tocopherol has -with a k_1 value of 320×10^4- more than twice the antioxidant potential of γ-tocopherol[7)]. The prior art data suggest either that the antioxidant potential of a compound is completely unrelated to the potential of the compound to influence processes in epithelial cells, or that the potential of the compound to influence processes in epithelial cells is strongly dependent on further factors such as, for example, the environment in which the compound is employed. In either event, the antioxidant potential of the compound cannot be regarded as an indication that the compound will exhibit any properties when it is applied to epithelial cells. The

7) It is respectfully noted that the section of ***Jiang et al.***'s disclosure which is referenced by the Examiner, cf. page 11495, col. 2, para. 3, cf. *"γ-T and γ-CEHC exhibit dose-dependent inhibition of PGE_2 release [in a human lung epithelial cancer cell line] .... α-T did not show any effect even at a concentration of 40 μM."*, fully corresponds to the information summarized in the first para. on page 11494.

foregoing compilation therefore shows that the disclosure of ***Burton et al.*** fails to add any information to the teaching of ***Jiang et al.*** which would motivate a person of ordinary skill in the art to apply α-CEHC to human skin or to human hair.

The Examiner further argues that ***Burton et al.*** teach various tocopherol compounds having antioxidant properties, including esters of α-CEHC, in carriers which would also be suitable as excipients in a dosage form and refers to the Court's decision in *In re Dillon*[8] for it's ruling that a new utility for an old and well known composition does not render such a composition new. It is respectfully noted that applicants' Claims 9 and 11 which relate to a cosmetic composition require the presence of α-CEHC rather than an ester of α-CEHC. It is also respectfully noted that the respective preparations investigated by ***Burton et al.*** cannot be deemed to provide the requisite compounds in carriers which are suitable for cosmetics. The respective preparations of ***Burton et al.*** included either styrene monomer or benzene which compounds are well known to be hazardous to the health of humans[9]. The circumstances here are, therefore, not deemed to be sufficiently similar to the situation which was addressed by the Court in *In re Dillon* where the prior art disclosed a gasoline mixture comprising an ortho ester and the claim was drawn to a gasoline mixture comprising a homolog of the ortho ester. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art and cannot be based on the applicant's disclosure[10] in a determination under Section 103(a). Neither the teaching of ***Jiang et al.*** nor the disclosure of ***Burton et al.*** provide for the necessary suggestion to do what applicants' have done. Moreover, the teaching of ***Jiang et al.*** and the disclosure of ***Burton et al.*** fail to provide for a reasonable expectation of success. In light of the foregoing and the arguments already presented in applicants' previous reply[11], the teaching of ***Jiang et al.*** when taken in view of the disclosure of ***Burton et al.*** cannot be considered to render applicants' invention obvious within the meaning of Section 103(a). It is therefore respectfully requested that the rejection be withdrawn. Favorable action is solicited.

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8) 919 F.2d 688, 16 USPQ2d 1897 (CAFC 1990), cert. denied, 500 U.S. 904 (1991)

9) See the attached copy of ***Hawley's*** *Condensed Chemical Dictionary*, 13th Ed., John Wiley & Sons, Inc. (1997), pages 123, 124, 1055 and 1056.

10) In re Vaeck, 947 F.2d 488, 20 USPQ2d 1438, 1442 (CAFC 1991)

11) Paper No. 05 dated October 31, 2003 (*date of the Certificate of Mailing*).

The Examiner has rejected Claims 3 to 9 and 11 under 35 U.S.C. §112, ¶1, as being as being drawn to subject matter which is insufficiently enabled by the information provided in the application. More particularly, the Examiner contends that applicants' disclosure is insufficient to enable a person of ordinary skill in the art to use a method which is effective in *"protecting human skin or human hair against aging processes"*. Favorable reconsideration of the Examiner's position is respectfully solicited in light of the revisions effected in the wording of Claims 3 and 9 and the following remarks:

Applicants have replaced the wording criticized by the Examiner by the phrase *"preventing or reducing the effects of aging processes or harmful environmental effects on the human skin or human hair"*. In accordance with the wording of Claim 3, the respective method comprises that an effective amount of the chroman of formula (Ia) is applied to the skin or the hair. Suitable application forms as well as effective amounts of the chroman are specifically addressed on page 6, indicated line 1, to page 18, indicated line 12, of the application. Additional exemplary preparations are provided on page 18, indicated line 18, to page 26, indicated line 24, of the application. Moreover, the use of skin care and hair care products is well known in the art, and it is well settled that for enablement under Section 112, ¶1, an application need not teach (*and preferably omits*) that which is well known in the art[12)].

The Examiner argues that *"the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity"* and criticizes that applicants have not included *"working examples"* corroborating the properties of the chroman (Ia) which are described in applicants' disclosure.

On the one hand, it is respectfully noted that the Examiner's respective position is diametrically opposed to the position taken by the Examiner in the determination under Section 103(a). What is and what is not known in the art determines the predictability in the art and, accordingly, whether the claimed subject matter is prima facie obvious. Correspondingly, what is and what is not known in the art determines which kind of information is necessary, and has to be provided in the application, to enable a person of ordinary skill as required under Section 112, ¶1. Accordingly, the determination under

12) For example Hybritech, Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 231 USPQ 81 (CAFC 1986).

Section 103(a) and the determination under Section 112, 1, have to be based on one and the same state of the art and technical background knowledge. The Examiner's position in the context of the rejection under Section 112, ¶1, is not deemed to be well taken in light of the position which the Examiner takes in his determination under Section 103(a).

On the other hand, the Examiner's position reflects that the Examiner doubts the truth and accuracy of applicants' statements in the application pertaining to the properties of the chroman (Ia). However, where the PTO raises such doubts it is incumbent on the Patent Office to provide acceptable evidence or reasoning why a person of ordinary skill in the art would reasonably doubt the truth and accuracy of statements made in the application[13)], particularly in light of the Declaration submitted by applicants upon filing. The Examiner's allegation that the art is unpredictable is not deemed to be acceptable evidence or reasoning, particularly since the allegation is opposed to the position taken by the Examiner in the rejection under Section 103(a). As such, the arguments made by the Examiner are not deemed to establish a *prima facie* case of lack of enablement. It is therefore respectfully requested that the rejection of Claims 3 to 9 and 11 under Section 112, ¶1, be withdrawn. Favorable action is solicited.

The Examiner has rejected Claims 3 to 8 under 35 U.S.C. §112, ¶2, contending that the claimed subject matter is rendered indefinite by the phrase *"protecting human skin or human hair against aging processes"*. Favorable reconsideration of the Examiner's position and withdrawal of the respective rejection is respectfully solicited in light of the revisions effected in the wording of Claim 3 and the following remarks:

The essential inquiry pertaining to definiteness requirement of Section 112, ¶2, is whether the claims set out and circumscribe a particular subject matter with a <u>*reasonable*</u> degree of clarity and particularity. Definiteness of claim language must be analyzed, not in a vacuum, but in light of:

(A) the content of the particular application disclosure;

(B) the teachings of the prior art; and

13) <u>In re Marzocchi</u>, 439 F.2d 220, 169 USPQ 637 (CCPA 1971).

(C) the claim interpretation that would be given by one possessing the ordinary level of skill in the pertinent art at the time the invention was made.

A person of ordinary skill in the art pertaining to cosmetics and dermatology is well acquainted with cosmetics and dermatological preparations which aim at counteracting the damaging effects of aging and damaging environmental effects on human hair and skin[14]. Therefore, and in light of applicants' disclosure, such a person of ordinary skill would not consider the wording *"[a] method for preventing ... the effects of aging processes or harmful environmental effects on human skin or human hair"* to mean that the respective effects are prevented completely for an indefinite amount of time. Rather, such a person of ordinary skill understands that prevention means that the onset of the respective effects is delayed, and would give applicants' claims the respective interpretation. Applicants have therefore replaced the wording criticized by the Examiner by the phrase *"preventing or reducing the effects of aging processes or harmful environmental effects on the human skin or human hair"*.

Applicants greatly appreciate the Examiner's suggestion to refer in the claims to *"masking the aging processes"*. The wording introduced by applicants expresses the same sentiment. Moreover, the wording introduced by applicants is consonant with the terminology used in the description and is, therefore, deemed to be less likely to give rise to claim interpretation problems.

In light of the foregoing and the attached it is therefore respectfully requested that the rejection of Claims 3 to 8 under Section 112, ¶2, be withdrawn. Favorable action is solicited.

REQUEST FOR EXTENSION OF TIME:

It is respectfully requested that a *two* month extension of time be granted in this case. A check for the *$420.00* fee is attached.

Please charge any shortage in fees due in connection with the filing of this paper, including Extension of Time fees, to Deposit

14) For example page 2, indicated lines 5 to 19, of the application.

Account No. 11.0345. Please credit any excess fees to such deposit account.

Respectfully submitted,
KEIL & WEINKAUF

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Encl.: THE LISTING OF CLAIMS (Appendix I)
Burton et al., J. Am. Chem. Soc. 107, 7053-7065 (1985)
Hawley's *Condensed Chemical Dictionary*, 13th Ed., John Wiley & Sons, Inc. (1997), pages 123, 124, 1055 and 1056

HBK/BAS

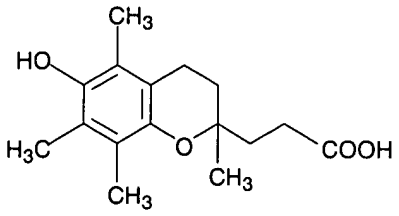
APPENDIX I:

THE LISTING OF CLAIMS:

1. (*canceled*)

2. (*canceled*)

3. (*currently amended*) A method for ~~protecting human skin or human hair against~~ preventing or reducing the effects of aging processes or harmful environmental effects on human skin or human hair which comprises applying to the skin or the hair an effective amount of a chroman of formula Ia



Ia.

4. (*previously presented*) The method of claim 3, wherein the chroman is applied for prophylaxis against aging processes of the human skin.

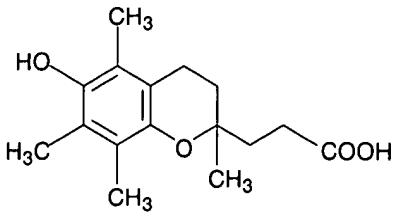
5. (*previously presented*) The method of claim 4, wherein the chroman is applied for prophylaxis against dry skin, wrinkle formation and/or pigment disorders.

6. (*previously presented*) The method of claim 3, wherein the chroman is applied for prophylaxis against aging processes of human hair.

7. (*previously presented*) The method of claim 3, wherein the effective amount of the chroman is applied by way of applying a cosmetic preparation.

8. (*previously presented*) The method of claim 7, wherein the cosmetic preparation contains the chroman in concentrations of from 0.01 to 30% by weight, based on the total amount of the cosmetic preparation.

9. (*currently amended*) A cosmetic preparation for ~~protecting~~ preventing or reducing the effects of aging processes or harmful environmental effects on the human epidermis or human hair, which comprises, in a cosmetically suitable carrier, a cosmetically effective amount of a chroman of formula Ia



Ia.

10. (*canceled*)

11. (*previously presented*) The cosmetic preparation defined in claim 9, which comprises the chroman in an amount of from 0.01 to 30% by weight, based on the total weight of the preparation.

PTO's copy

Hawley's

Condensed Chemical

Dictionary

THIRTEENTH EDITION

Revised by

Richard J. Lewis, Sr.

JOHN WILEY & SONS, INC.
New York • Chichester • Weinheim • Brisbane • Singapore • Toronto

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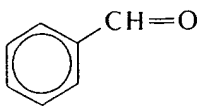
benzaldehyde. (benzoic aldehyde; synthetic oil of bitter almond).
CAS: 100-52-7. C_6H_5CHO.



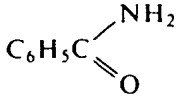
Properties: Colorless or yellowish, strongly refractive, volatile oil; odor resembling oil of bitter almond; burning aromatic taste. Oxidizes readily. D 1.0415 (25/4C), refr index 1.5440–1.5464 at 20C, fp −56C; bp 178C, flash p 145F (62.7C) (CC). Miscible with alcohol, ether, fixed and volatile oils; slightly soluble in water. Oxidizes in air to benzoic acid. Combustible. Autoign temp 377F (191.6C).
Derivation: (1) Air oxidation of toluene with uranium or molybdenum oxides as catalysts; (2) reaction of benzyl dichloride with lime; (3) extraction from oil of bitter almond.
Impurities: Usually chlorides.
Method of purification: Rectification.
Grade: Technical, NF. *Note:* The specifications, especially regarding impurities, vary considerably for the grades used for dye manufacture from those used in perfumery.
Hazard: Highly toxic.
Use: Chemical intermediate for dyes, flavoring materials, perfumes, and aromatic alcohols; solvent for oils, resins, some cellulose ethers, cellulose acetate and nitrate; flavoring compounds; synthetic perfumes; manufacturing of cinnamic acid, benzoic acid; pharmaceuticals; photographic chemicals.

benzaldehyde cyanohydrin. See mandelonitrile.

benzaldehyde green. See Malachite green.

benzalkonium chloride. A mixture of alkyl dimethylbenzylammonium chlorides of general formula $C_6H_5CH_2N(CH_3)_2RCl$ in which R is a mixture of the alkyls from C_8H_{17} to $C_{18}H_{37}$. It is a typical quaternary ammonium salt.
Properties: White or yellowish-white, amorphous powder or gelatinous pieces; aromatic odor; very bitter taste. Soluble in water, alcohol, or acetone; almost insoluble in ether; slightly soluble in benzene. Water solutions foam strongly when shaken and are alkaline to litmus.
Grade: USP.
Hazard: Highly toxic.
Use: Cationic detergent; surface antiseptic; fungicide.

benzamide. (benzoylamide). $C_6H_5CONH_2$.



Properties: Colorless crystals. Mp 130C, bp 288C, d 1.341. Soluble in hot water, hot benzene, alcohol, and ether. Combustible.
Derivation: From benzoyl chloride and ammonia or ammonium carbonate.
Grade: Technical.
Use: Organic synthesis.

benzaminoacetic acid. See hippuric acid.

benzanilide. (benzoylaniline; phenylbenzamide). $C_6H_5NH(COC_6H_5)$.
Properties: White to reddish crystals and powder. Related to acetanilide, containing benzoyl in place of acetyl radical. D 1.306, mp 160–162C. Soluble in alcohol; insoluble in water; slightly soluble in ether.
Derivation: From benzoic anhydride and aniline with sodium hydroxide.
Use: Intermediate in the synthesis of dyes, drugs, and perfumes.

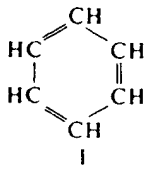
benzanthrone. $C_{17}H_{10}O$. A four-ring system.
Properties: Pale-yellow needles. Mp 170C. Soluble in alcohol and other organic solvents.
Derivation: (1) From anthranol and glycerol via condensation via sulfuric acid (anthranol is made from anthraquinone), (2) from anthracene in sulfuric acid solution by addition of glycerol and heating to 100–110C until the anthracene disappears. The reaction mass is then diluted with water, salted out, and purified.
Method of purification: Crystallization from toluene.
Use: Dyes.

benzathine penicillin G. (*N,N'*-dibenzylethylenediamine dipenicillin G).
$2C_{16}H_{18}N_2O_4S{\cdot}C_{16}H_{20}N_2{\cdot}4H_2O$.
Properties: White crystalline powder; odorless. The pH of a saturated solution is 4.5–7.5. Slightly soluble in alcohol; almost insoluble in water.
Grade: USP.
Use: Medicine (antibiotic).

benzazimide. See 4-ketobenzotriazine.

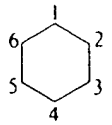
"Benzedrine" *[SmithKline].* TM for amphetamine sulfate.

benzene.
CAS: 71-43-2. C_6H_6. 16th highest-volume chemical produced in U.S. (1995).



I


II



III


IV

Structure: I. Complete ring showing all elements.
II. Standard ring showing double bonds only.
III. Simple ring without double bonds, with numerals indicating position of carbon atoms to which substituent atoms or groups may be attached (2 = ortho, 3 = meta, 4 = para).
IV. Generalized structure with enclosed circle suggesting the resonance of this compound. This structure is now in general use.
These structures are also referred to as the benzene nucleus.

Properties: Colorless to light-yellow; mobile; nonpolar liquid of highly refractive nature; aromatic odor. Bp 80.1C, fp 5.5C, d 0.8790 (20/4C), wt/gal 7.32 lb, refr index 1.50110 at 20C, flash p 12F (−11C) (CC), surface tension 29 dynes/cm; autoign temp 1044F (562C). Miscible with alcohol, ether, acetone, carbon tetrachloride, carbon disulfide, acetic acid; slightly soluble in water. Vapors burn with smoky flame.

Derivation: (1) Hydrodealkylation of toluene or pyrolysis of gasoline; (2) transalkylation of toluene by disproportionation reaction; (3) catalytic reforming of petroleum; (4) fractional distillation of coal tar.

Grade: Crude, straw color, motor, industrial pure (2C), nitration (1C), thiophene-free, 99 mole %, 99.94 mole %, nanograde.

Hazard: A carcinogen. Highly toxic. Flammable, dangerous fire risk. Explosive limits in air 1.5 to 8% by volume. TLV: 10 ppm in air.

Use: Manufacturing of ethylbenzene (for styrene monomer), dodecylbenzene (for detergents), cyclohexane (for nylon), phenol, nitrobenzene (for aniline), maleic anhydride, chlorobenzene, diphenyl, benzene hexachloride, benzene-sulfonic acid, and as a solvent.

See aromatic.

benzene azimide. See 1,2,3-benzotriazole.

benzeneazoanilide. See diazoaminobenzene.

benzeneazobenzene. See azobenzene.

benzeneazo-*p*-benzeneazo-*β*-naphthol. ("Sudan" III; tetraazobenzene-*β*-naphthol). $C_{22}H_{16}ON_4$. A red dye; CI 26100.444.

Properties: Brown powder. Mp 195C. Insoluble in water; soluble in alcohol, oils, chloroform, glacial arctic acid.

Use: Coloring oils red; biological stain.

benzeneazonaphthylethylenediamine. See azodine.

benzenecarboxylic acid. See benzoic acid.

benzenediazonium chloride. $C_6H_5N(N)Cl$.

Properties: Ionic salt. Very soluble in water; insoluble in most organic solvents.

Hazard: Highly toxic. Can explode on heating.

Use: Dye intermediate.

benzene dibromide. See dibromobenzene.

1,3-benzenedicarbonitrile. See *m*-phthalodinitrile.

benzene-*o*-dicarboxylic acid. See phthalic acid.

benzene-*p*-dicarboxylic acid. See terephthalic acid.

benzene hexachloride. (BHC). A commercial mixture of isomers of 1,2,3,4,5,6-hexachlorocyclohexane.

Hazard: The *γ*-isomer is highly toxic. Use may be restricted.

Use: An insecticide.

See lindane.

benzenemonosulfonic acid. See benzenesulfonic acid.

benzenephosphinic acid. (phenylphosphinic acid). $C_6H_5H_2PO_2$.

Properties: Colorless crystals. Mp 82–84C, d 1.376 (29C). Decomposes at 200C. Stable in air. Soluble in water, alcohol, acetone; slightly soluble in ether; insoluble in benzene, hexane, CCl_4. Combustible.

Use: Antioxidant; intermediate for metallic-salt formation; accelerator for organic peroxide catalysts.

benzenephosphonic acid. (phenylphosphonic acid). $C_6H_5H_2PO_3$.

Properties: Colorless crystals. Mp 158C, d 1.475 (4C), decomposes at 275C. Soluble in water, alcohol, CCl_4. Combustible.

Hazard: Highly toxic.

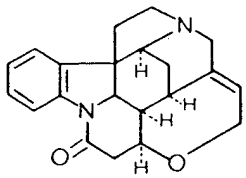
Use: Intermediate in antifouling paint agents; catalyst in organic reactions.

benzenephosphorus dichloride. $C_6H_5PCl_2$.

Properties: Highly reactive, colorless liquid. Mp −51C, bp 224.6C, d 1.315 (25C), refr index 1.5958 (25C). Soluble in common inert organic solvents. Fumes in air; hydrolyzes in water.

Properties: Colorless crystals. Mp 256C.
Use: Reagent for nitrate determination.

strychnine.
CAS: 57-24-9. $C_{21}H_{22}N_2O_2$. An alkaloid.



Properties: Hard white crystals or powder; bitter taste. Mp 268–290C, bp 270C (5 mm Hg). Soluble in chloroform; slightly soluble in alcohol and benzene; slightly soluble in water and ether.
Derivation: Extraction of the seeds of *Nux vomica* with acetic acid, filtration, precipitation by alkali and filtration.
Grade: Crystals, powder, technical.
Hazard: Toxic by ingestion and inhalation. TLV: 0.15 mg/m³ of air.
Use: Pesticide.

stuff. Term used by papermakers to refer to the aqueous pulp suspension fed onto the fourdrinier wire from the headbox.
See furnish.

Stuffer disulfone hydrolysis rule. (1) All sulfones containing vicinal sulfone group–substituted carbon atoms (γ-disulfones) are hydrolyzed by dilute alkali with formation of β-hydroxysulfone and sulfinate. (2) All sulfones in which adjacent carbon atoms carry a strongly negative group, and one or two sulfone residues can be cleaved into a sulfinic acid and an unsaturated compound.

"STXS" *[Vista].*
Available forms: Liquid. TM for sodium, toluene, xylene, sulfonate.
Use: A hydrotrope or solubilizing agent in detergent formulas.

"Stymer" Vinyl Styrene *[Monsanto].* TM for resins used as sizes for filament acetates. L.F. A vinyl resin. Soluble with ammonium hydroxide, sulfur. Styrene copolymer resin. Soluble in water.

S-type synthetic elastomer. See styrene-butadiene rubber.

styphnic acid. (2,4,6-trinitroresorcinol).
CAS: 82-71-3. $C_6H(OH)_2(NO_2)_3$.
Properties: Yellow crystals; astringent taste. Mp 179–180C. Soluble in alcohol and ether; slightly soluble in water. An initiating explosive. Forms additional compounds with many hydrocarbons.
Derivation: Nitration of resorcinol.
Hazard: Severe explosion risk when heated.
Use: Priming agents in the explosives industry.

styracin. See cinnamyl cinnamate.

styralyl acetate. See α-methylbenzyl acetate.

styralyl alcohol. See α-methylbenzyl alcohol.

styrax. A type of balsam found in Central America and the Near East.
See balsam.

styrenated oil. A drying oil whose drying and hardening characteristics have been modified by incorporation of styrene or a similar monomer.

styrene. See polystyrene; styrene monomer.

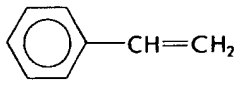
styrene-acrylonitrile. See polystyrene.

styrene-butadiene rubber. (SBR). By far the most widely used type of synthetic rubber, its consumption for all applications is four times that of polybutadiene, its nearest competitor, and 1.5 times that of all other elastomers combined. Its manufacture involves copolymerization of three parts butadiene with one part styrene. These materials are suspended in finely divided emulsion form in a large proportion of water, in the presence of a soap or detergent. Also present in small amounts are an initiator or catalyst which is usually a peroxide, and a chain-modifying agent such as dodecyl mercaptan.
Use: Tires, footwear, mechanical goods, coatings, adhesives, solvent-release sealants, carpet backing.
See rubber, synthetic; polymerization; free radical.

styrene glycol.
CAS: 93-56-1. $C_8H_{10}O_2$.
Properties: Acicular crystals. Mp 67C, bp 272C. Soluble in water and organic solvents.
Use: Plasticizers.

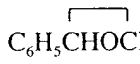
styrene monomer. (vinylbenzene; phenylethylene; cinnamene).
CAS: 100-42-5. $C_6H_5CH{:}CH_2$. 20th highest-volume chemical produced in U.S. (1995).
Properties: Colorless, oily liquid; aromatic odor. Fp −30.63C, bp 145.2C, d 0.9045 (25/25C), bulk d 7.55 lbs/gal (20C), flash p 88F (31.1C), autoign temp 914F (490C). Insoluble in water; soluble in alcohol and ether. Readily undergoes polymerization when heated or exposed to light or a peroxide catalyst; the polymerization releases heat and may become explosive.
Derivation: From ethylene and benzene in the presence of aluminum chloride to yield ethylbenzene, which is catalytically dehydrogenated at 630C to form styrene.

Grade: Technical 99.2%, polymer 99.6%.
Hazard: Flammable, moderate fire risk, explosive limits in air 1.1–6.1%, must be inhibited during storage. Toxic by ingestion and inhalation. TLV: 50 ppm in air.
Use: Polystyrene; SBR, ABS, and SAN resins; protective coatings (styrene-butadiene latex, alkyds); styrenated polyesters; rubber-modified polystyrene; copolymer resins; intermediate.



styrene nitrosite. A compound resulting from the reaction between styrene and nitrogen dioxide and used as a qualitative or quantitative specific test for monomeric styrene in mixtures with other hydrocarbons.

styrene oxide.
CAS: 96-09-3.



$C_6H_5CHOCH_2$.

Properties: Colorless to pale-straw-colored liquid. Boiling range 194.2–195C (5–95%), fp −36.6C, flash p 180F (82.2C) (COC), refr index 1.5328 (25C), d 1.0469 (25/4C). Miscible with benzene, acetone, ether, and methanol. Combustible.
Hazard: Toxic by ingestion and inhalation.
Use: Highly reactive organic intermediate.

"Styresol" ***[Reichhold].*** TM for a group of styrenated alkyd resins with air-drying and baking properties and high resistance to gasoline, alkalies, acids, and water.

"Styrofoam" ***[Dow].*** TM for expanded cellular polystyrene (available in colors).
Use: Insulating materials; light-weight materials for boats, toys, etc.; separators in packing containers; airport runways; highway construction; battery cases.

"Styron" ***[Dow].*** TM for polystyrene resins, general purpose, medium and high impact, heat and impact-heat resistant, and light-stabilized resins ("Styron Verelite"). Available in wide range of translucent and opaque colors, as well as natural and crystal.
Use: Packaging, toys, appliance parts, bottle closures and containers, hot and cold drinking cups, television cabinet backs, automotive components and machine housings, lighting equipment.

styryl carbinol. See cinnamic alcohol.

suberane. See cycloheptane.

suberic acid. (octanedioic acid).
$HOOC(CH_2)_6COOH$.
Properties: Colorless crystals from water. Mp 143C, bp 279C (100 mm Hg). Partially soluble in water and ether; soluble in alcohol. Combustible.
Derivation: Oxidation of oleic acid with nitric acid.
Use: Intermediate for the synthesis of drugs, dyes, and high polymers.

suberone. See cycloheptanone.

"Sublaprints" ***[Holliday].*** TM for uncut disperse dyestuffs.
Use: In transfer printing applications.

sublimation. The direct passage of a substance from solid to vapor without appearing in the intermediate (liquid) state. An example is solid carbon dioxide which vaporizes at room temperature; the conversion may also be from vapor to solid under appropriate conditions of temperature.

subnuclear particle. A particle either found in the nucleus or observed coming from the nucleus as the result of nuclear reaction or rearrangement, i.e., neutrons, mesons, etc.

substance. Any chemical element or compound. All substances are characterized by a unique and identical constitution and are thus homogeneous. "A material of which every part is like every other part is said to be homogeneous and is called a substance." (Black and Conant, *Practical Chemistry.*) See homogeneous.

substantive dye. See direct dye.

substituent. An atom or radical that replaces another in a molecule as the result of a reaction. See substitution.

substitute natural gas. See synthetic natural gas.

substitution. The replacement of one element or radical by another as a result of a chemical reaction. Chlorination of benzene to produce chlorobenzene is a typical example; in this case a chlorine atom replaces a hydrogen atom in the benzene molecule.

substrate. (1) A substance upon which an enzyme or ferment acts. (2) Any solid surface on which a coating or layer of a different material is deposited.

subtilin. An antibiotic produced by the metabolic processes of a strain of *Bacillus subtilis.* It is a cyclic polypeptide similar to bacitracin in chemical structure and antibiotic activity, but not as important clinically. Subtilin is active against many Gram-positive bacteria, some Gram-negative cocci, and some species of fungi. It is a surface tension

PTO's copy

6 ne) λ_{max} 255 (ϵ 24 800), 265 (33 700), and 276 (27 000).

Irradiation of Trienes. The general procedure was to prepare solutions of the particular triene in cyclohexane at concentrations on the order of 0.07–0.08 M containing a known amount of *n*-tridecane as internal standard for GLC analysis. The solutions were irradiated at various wavelengths from 300–350 nm and samples were periodically withdrawn for GLC analysis at intervals of 5 min to 1 h on a 14 ft × $^1/_8$ in. column of 10% Carbowax 20M on 80–100 mesh Chromosorb P. Ultimately, irradiations were carried out on an optical bench with 313-nm light isolated from the output of a high-intensity mercury lamp, using either a solution filter combination of 0.5% w/v potassium hydrogen phthalate in water (1 cm) 15% w/v $KCr(SO_4)_2 \cdot 12H_2O$ in 1.0 N H_2SO_4 (2 cm)[48] or a grating monochromator. Details on the distribution of trienes obtained in these irradiations are to be found in ref 42.

Irradiation of Cycloheptadienones. In a typical experiment, a solution of 42.5 mg (3.1×10^{-4} mol) of dienone **2** in 5 mL of cyclohexane was prepared, 180 μL of a 0.01 M solution of *n*-tridecane in cyclohexane was added, and the solution was purged with nitrogen and irradiated at 313 nm (see above) at 20 °C with use of a Pyrex filter. The course of reaction was monitored by GLC, using a 14 ft × $^1/_8$ in. column of 10% Carbowax 20 M on 80–100 mesh Chromosorb P at an oven temperature of 115 °C and a flow rate of 30 mL/min. The results are given in the Results section. Entirely analogously experiments were made with use of dienone **1**.

(48) Parker, C. A. "Photoluminescence in Solution"; Elsevier: New York, 1968; pp 186–190.

Acknowledgment. This study was supported in part by Grant CHE-7819750 from the National Science Foundation. We are grateful to a number of colleagues for their help and their criticisms, including Professors S. R. Wilson, W. C. Agosta, and J. A. Berson and Drs. David A. Dunn and Angelo C. Brisimitzakis. We are also grateful to two of the referees for their constructive suggestions based on a very thorough reading of the original manuscript.

Registry No. 1, 85236-00-6; **1** (adduct with **7**), 87362-95-6; **2**, 85236-01-7; **2** (adduct with **7**), 87420-92-6; **3a**, 42104-03-0; **3b**, 36269-78-0; **4**, 29639-53-0; **5**, 87362-94-5; **7**, 4233-33-4; **8**, 14947-19-4; **9**, 2417-80-3; **10**, 14947-20-7; **11**, 15192-80-0; $HC{\equiv}CCH_2CH(OSO_2C_6H_4\text{-}p\text{-}CH_3)CH_3$, 58456-48-7; $(Z)\text{-}H_3CCH{=}CHC{\equiv}CH$, 1574-40-9; $(E)\text{-}H_3CCH{=}CHC{\equiv}CH$, 2004-69-5; $(Z)\text{-}H_3CCH{=}CHC{\equiv}CCH_2CH(OH)CH_3$, 52944-44-2; $(E)\text{-}H_3CCH{=}CHC{\equiv}CCH_2CH(OH)CH_3$, 52944-45-3; $(Z,E)\text{-}H_3CCH{=}CHCH{=}CHCH_2CH(OH)CH_3$, 52944-46-4; $(Z,Z)\text{-}H_3CCH{=}CHCH{=}CHCH_2CH(OH)CH_3$, 52944-47-5; $(Z,E)\text{-}H_3CCH(OSO_2C_6H_4\text{-}p\text{-}CH_3)CH_2CH{=}CHCH{=}CHCH_3$, 58822-86-9; $(Z,Z)\text{-}H_3CCH(OSO_2C_6H_4\text{-}p\text{-}CH_3)CH_2CH{=}CHCH{=}CHCH_3$, 58822-87-0; tropone, 539-80-0.

Supplementary Material Available: Four tables of X-ray data for the adduct of PTAD and dienone **1**, including fractional coordinants, thermal parameters, bond distances, and bond angles (4 pages). Ordering information is given on any current masthead page.

Autoxidation of Biological Molecules. 4. Maximizing the Antioxidant Activity of Phenols[1]

G. W. Burton, T. Doba,[2] E. J. Gabe, L. Hughes, F. L. Lee, L. Prasad, and K. U. Ingold*

Contribution from the Division of Chemistry, National Research Council of Canada, Ottawa, Ontario, Canada K1A 0R6. *Received April 5, 1985*

Abstract: Rate constants, k_1, for H-atom abstraction by peroxyl radicals from α-tocopherol and 35 structurally related phenols have been measured at 30 °C by the inhibited autoxidation of styrene (IAS) method. An independent laser-flash kinetic EPR method was used with ten of these phenols which gave k_1 values at 24 °C that were in satisfactory agreement with the values found by the IAS method. The structures of several phenols were determined by X-ray analysis. The EPR spectral parameters for the phenoxyl radicals derived from many of these phenols were also measured. The relative magnitudes of k_1 values for phenols that are structurally closely related and have an oxy substituent para to the hydroxyl group can be correlated with the degree of stabilization of the phenoxyl radical. Stabilization depends on two factors: (i) the extent of orbital overlap between the 2p type lone pair on the para oxygen atom and the aromatic π electron system and (ii) the electron-donating or withdrawing character of the group bonded to the para oxygen atom. Orbital overlap depends on the dihedral angle, θ, between the direction of the 2p orbital on the para oxygen and a line perpendicular to the aromatic plane. It can be estimated from the X-ray structures. Along the series 4-methoxytetramethylphenol (VIc), 6-hydroxy-2,2,5,7,8-pentamethylchromene, 6-hydroxy-2,2,5,7,8-pentamethylchroman, and 2,3-dihydro-5-hydroxy-2,2,4,6,7-pentamethylbenzofuran (IIIb), k_1 increases from 3.9×10^5, 2.5×10^6, 3.8×10^6, to 5.7×10^6 M^{-1} s^{-1}, as θ decreases from 89, 38, 17, to 6°. Compound IIIb is the most active antioxidant being 1.8 times more active than α-tocopherol. For 2-substituted 6-hydroxy-2,5,7,8-tetramethylchromans log (k_1/M^{-1} s^{-1}) can be correlated with the σ_I constant of the 2-substituent, $\rho_I = -1.25$. For these compounds and for some 2,6-dimethylphenols log (k_1/M^{-1} s^{-1}) can also be correlated with the extent of stabilization of the corresponding phenoxyl radicals as measured by the unpaired spin density at the two ortho methyl groups. Some additional kinetic and spectroscopic data are presented. It is also shown that the perpendicular methoxy group in VIc is not deactivating relative to a hydrogen atom but is, instead, about as activating as a methyl group.

α-Tocopherol (α-T) is not only the most biologically active component of vitamin E but, as we have previously reported,[1c,3] it is also one of the best chain-breaking, phenolic antioxidants known. That is, α-T and a number of structurally related model compounds react more rapidly with peroxyl radicals (reaction 1) than do otherwise similar phenols that lack the fused 6-membered heterocyclic ring. We have concluded[3] that stereoelectronic effects

$$ROO\cdot + ArOH \xrightarrow{k_1} ROOH + ArO\cdot \qquad (1)$$

conferred on α-T by this ring are largely responsible for the high reactivity of α-tocopherol and related compounds. The heterocyclic ring ensures that the 2p-type lone pair of electrons on the ring oxygen adopts an orientation more or less perpendicular to the plane of the aromatic ring and, in this orientation, this 2p-type lone pair stabilizes the developing phenoxyl radical.[3] The superior antioxidant behavior of α-T is further supported by our finding

(1) (a) Issued as NRCC No. 24983. (b) Part 3: Burton, G. W.; Joyce, A.; Ingold, K. U. *Arch. Biochem. Biophys.* **1983**, *221*, 281–290. For preliminary accounts of portions of this work, see: (c) Burton, G. W.; Hughes, L.; Ingold, K. U. *J. Am. Chem. Soc.* **1983**, *105*, 5950–5951. (d) Doba, T.; Burton, G. W.; Ingold, K. U. *Ibid.* **1983**, *105*, 6505–6506. (e) Doba, T.; Burton, G. W.; Ingold, K. U.; Matsuo, M. *J. Chem. Soc., Chem. Commun.* **1984**, 461.

(2) NRCC Research Associate 1982–1985.

(3) (a) Burton, G. W.; Le Page, Y.; Gabe, E. J.; Ingold, K. U. *J. Am. Chem. Soc.* **1980**, *102*, 7791–7792. (b) Burton, G. W.; Ingold, K. U. *Ibid.* **1981**, *103*, 6472–6477.

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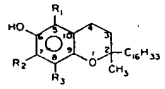
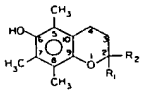
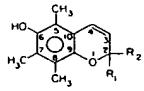
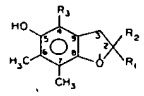
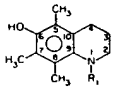
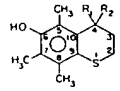
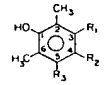
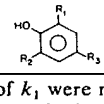
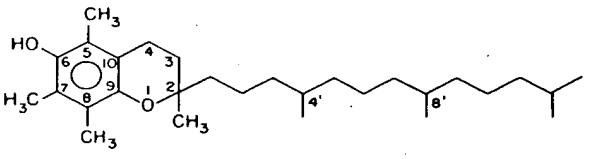
Table I. Structures, Identifying Symbols (IS), and Values of k_1 for Selected Phenolic Antioxidants[a]

structure	R_1	R_2	R_3	IS	10^4k_1 (M^{-1} s^{-1})[b] IAS	LKEPR
	H	H	CH_3	δ-T	44	33
	H	CH_3	CH_3	γ-T	140	70
	CH_3	H	CH_3	β-T	130	
	CH_3	CH_3	CH_3	α-T	320	260
	CH_3	CH_3	H	DMT	180	
	H	H		Ia	270	
	CH_3	CH_3		Ib	380	
	CH_3	C(O)OH		Ic	110	
	CH_3	C(O)OCH3		Id	180	
	CH_3	$CH_2C(O)OH$		Ie	190	
	CH_3	$CH_2C(O)OCH_3$		If	270	
	CH_3	$(CH_2)_2C(O)OH$		Ig	370	
	CH_3	$(CH_2)_2C(O)OCH_3$		Ih	330	
	CH_3	CH_2OH		Ii	270	
	CH_3	OCH_3		Ij	150	
	CH_3	CH_3		IIa	250	200
	CH_3	$CH_2C(O)OH$		IIb	100	
	H	CH_3	CH_3	IIIa	540	
	CH_3	CH_3	CH_3	IIIb	570	
	CH_3	C(O)OH	CH_3	IIIc	160	
	CH_3	CH_3	H	IIId	320	
	H			IVa		
	$C(O)CH_3$			IVb	12	
	CH_2CH_3			IVc	200	200
	CH_3	CH_3		V	280	180
	H	OCH_3	H	VIa	94	
	H	OCH_3	CH_3	VIb	130	
	CH_3	OCH_3	CH_3	VIc	39	28
	CH_3	CH_3	CH_3	VId	36	
	CH_3	CH_3	H	VIe	11	
	H	CH_3	H	VIf	8.5	
	CH_3	H	CH_3	VIg	7.5	6.9
	H	H	H	VIh	2.5	
	$(CH_3)_3C$	$(CH_3)_3C$	CH_3O	VIIa	11	11
	$(CH_3)_3C$	$(CH_3)_3C$	CH_3	VIIb	1.4	2.4
	$(CH_3)_3C$	$(CH_3)_3C$	H	VIIc	0.31	

[a] Values of k_1 were measured by the inhibited autoxidation of styrene (IAS) at 30 °C method and by the laser/kinetic EPR (LKEPR) method at 24 °C. [b] For each phenol k_1 was measured in 2–15 independent experiments. For the IAS measurements the spread in k_1 values was <±10% in every case. For the LKEPR measurements the spread was generally <±15%.

that it accounts for most, if not all, of the antioxidant activity of the lipid fraction of human blood plasma and red blood cells.[1b]



α-Tocopherol (α-T)

The following question still remains: are chain-breaking antioxidant structural features fully optimized in α-tocopherol? More specifically, is the stereoelectronic effect maximized in α-T or are there other structures that express the effect more fully? Furthermore, what other features and/or properties does α-T possess that make it the major lipid-soluble, biological chain-breaking antioxidant? We have approached these questions from the chemical, or in vitro, side by synthesizing a wide variety of phenols structurally related to α-tocopherol and have measured their absolute reactivities toward peroxyl radicals, i.e., we have measured values for k_1. For some of these compounds k_1 values have been measured by two quite independent techniques. These kinetic data have then been correlated with structural features, some of our compounds having also been examined by X-ray crystallography. Other properties of these materials have also been examined such as the EPR spectra of the corresponding phenoxyl radicals, the self-reactions of these phenoxyls, and their (non)reaction with molecular oxygen. These in vitro studies have been designed to "set the stage" for a planned series of in vivo experiments in which we will examine the vitamin E activities and biokinetic properties of certain synthetic compounds relative to those of natural (2*R*,4′*R*,8′*R*)-α-tocopherol.

Results

The phenols examined in this work are divided for convenience into the 8 classes shown in Table I. These classes are the following: the tocopherols, δ-T–α-T and 5,7-dimethyltocol, DMT; the 6-hydroxy-5,7,8-trimethylchromans, Ia–Ij; the related chromenes, IIa and IIb; the 5-hydroxy-6,7-dimethyl-2,3-dihydrobenzofurans, IIIa–IIId; the 6-hydroxy-5,7,8-trimethyl-1,2,3,4-tetrahydroquinolines, IVa–IVc; a 6-hydroxy-5,7,8-trimethyl-3,4-dihydrobenzothiopyran, V; the 2,6-dimethylphenols, VIa–VIh; and the 2,6-di-*tert*-butylphenols, VIIa–VIIc. The numbering systems used with these compounds are also shown on the structures in this table.

Measurement of k_1 Values. Inhibited Autoxidation of Styrene (IAS) Method. Absolute values of k_1 were obtained for all the

henols listed in Table I by using them to inhibit the azobis-sobutyronitrile) (AIBN) thermally initiated autoxidation of yrene at 30 °C and measuring the rate of autoxidation during ie initial portion of the induction period.[3-9] The advantages of yrene as the oxidizable substrate have been enumerated.[3b] If ppropriate precautions are taken, this is by far the simplest ocedure for measuring k_1 values. The IAS method is also the ost versatile in terms of the range in k_1 values that can be termined, and furthermore, it is highly reliable and reproducible. o obtain good kinetic data it is essential that a sufficiently low te of chain initiation be employed for there to be an appreciable ain length for autoxidation even at the beginning of the induction riod. In addition, the apparatus must be sufficiently sensitive measure very small rates of oxygen absorption ($\sim 1 \times 10^{-9}$ M) with high precision. All our measurements of k_1 by this ocedure have been carried out at chain lengths >4. We have so greatly improved the sensitivity of our oxidation apparatus mpared with that used in our original kinetic studies on the copherols[3] (see Experimental Section). Results are given in able I. Despite its many advantages, the inhibited autoxidation styrene method does suffer from the fact that k_1 is not itself rectly measured. That is, the rate of oxidation during the duction period can be represented by

$$\frac{-d[O_2]}{dt} = \frac{k_2[C_6H_5CH{=}CH_2]R_i}{nk_1[ArOH]}$$

here R_i is the rate of chain initiation, the concentrations refer the time at which the rate of oxidation is measured, n is the mber of oxidation chains terminated per molecule of ArOH, d k_2 is the rate constant for the chain propagation step:

$$POO\cdot + C_6H_5CH{=}CH_2 \rightarrow POOCH_2\dot{C}HC_6H_5 \qquad (2)$$

this equation POO· represents the poly(peroxystyryl)peroxyl dical. Thus, at a known R_i (which can be readily determined the induction period method[1b,3-10]), the measured rate of oxation actually yields the rate constant ratio k_2/nk_1. The stoiometric factor, n, has been shown to be 2.0, or very close to), for the majority of phenolic antioxidants[3-6,10-12] including, particular, α-tocopherol[3,12] under the conditions commonly ployed in kinetic experiments. The accuracy of the absolute lues of k_1 that have been measured by the IAS method will refore ultimately depend on the accuracy of the measured value k_2 at 30 °C. We used the reported value[13] of 41 M^{-1} s^{-1} for

In 1981 we pointed out[3b] that literature values for k_1 for α-T ich had been measured by such varied techniques as oxygen sorption, chemiluminescence, and pulse radiolysis covered the prisingly wide range 2.0×10^5 to 2.3×10^7 M^{-1} s^{-1} for al-lperoxy radicals.[14] There has been only a slight improvement this situation over the intervening years. Briefly, a chemiluminescence method has been reported[15] to yield k_1(C$_6$H$_5$CH(CH$_3$)OO· + α-T) = 1.5×10^5 M^{-1} s^{-1} at 25 °C; a pulse radiolysis method has revised k_1(c-C$_6$H$_{11}$OO· + α-T) from 2.3×10^7 M^{-1} s^{-1} [16] down to 7.9×10^6 M^{-1} s^{-1} [17] at room temperature; and the inhibited autoxidation method with methyl linoleate as the oxidizable substrate has yielded a value of 5.1×10^5 M^{-1} s^{-1} at 37 °C.[18,19] These values should be compared with our original value[3] for k_1(POO· + α-T) of 2.4×10^6 M^{-1} s^{-1} at 30 °C and our current revised value[1c] of 3.2×10^6 M^{-1} s^{-1}. There is fairly strong evidence[21-25] to suggest that k_1 values do not to any great extent depend on the structure of the alkylperoxyl radical.[14] It therefore seemed desirable to check some of our IAS k_1 values with use of an independent technique.

Laser-Flash Kinetic EPR (LKEPR) Method. The pulse from a nitrogen laser was focussed on a sample in the cavity of an EPR spectrometer which contained di-*tert*-butyl ketone and a phenol in an oxygen-saturated hydrocarbon solvent.[24-27] Peroxyl radicals are formed in an essentially instantaneous process[28] by the reaction sequence,

$$(Me_3C)_2C{=}O \xrightarrow{h\nu} Me_3C\cdot + Me_3C\dot{C}{=}O \qquad (3)$$

$$Me_3C\cdot + O_2 \rightarrow Me_3COO\cdot \qquad (4)$$

$$Me_3C\dot{C}{=}O + O_2 \rightarrow Me_3CC(O)OO\cdot \qquad (5)$$

By a careful choice of spectrometer settings and other experimental conditions (see Experimental Section) it was possible, for phenols less reactive than α-T, to monitor the decay of the peroxyl radical signal under conditions of (pseudo) first-order kinetics without interference from the growth of the phenoxyl radical signal. Values of k_1 for the reaction of α-T and a number of less reactive phenols with the mixture of *tert*-butylperoxyl and pivaloylperoxyl radicals formed in this system are given in Table I. They were calculated from the relation,

$$k_1 = \ln 2/n[ArOH]\tau_{1/2}$$

where $\tau_{1/2}$ is the peroxyl radical half-life. It was assumed that $n = 1.0$ since any peroxyl/phenoxyl reaction should be unimportant in this system during the early stages of the peroxyl radical decay. The agreement with the results obtained by the IAS method is satisfactory considering the fact that the peroxyl radicals used in the two experiments really are quite different and in view of all the potential experimental errors and uncertainties.[14b]

For phenols that were more reactive than α-T it was necessary to work with very low concentrations of phenol in order to obtain a decay trace that did not merely reflect the time constant of the system. Sample depletion, even during a single pulse, then became a significant problem and reliable LKEPR k_1 values could not be determined.

Deuterium Kinetic Isotope Effect. Reaction 1 has been written

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(14) (a) We specifically exclude $Cl_3COO\cdot$ and related radicals having tron-withdrawing atoms or groups attached ot the α-carbon since such cies are known to be very much more reactive than alkylperoxyl radicals ard a variety of reagent. See, e.g., Packer et al. (Packer, J. E.; Slater, T. Willson, R. L. *Nature (London)* **1979**, *278*, 737–738) which for $Cl_3COO\cdot$ -T gives $k_1 = 5 \times 10^8$ M^{-1} s^{-1}. See also: Packer, J. E.; Willson, R. L.; nemann, D.; Asmus, K.-D. *J. Chem. Soc., Perkin Trans. 2* **1980**, 296–299. lfenden, B. S.; Willson, R. L. *Ibid.* **1982**, 805–812. Mönig, J.; Asmus, D.; Schaeffer, M.; Slater, T. F.; Willson, R. L. *Ibid.* **1983**, 1133–1137. (b) eferee has pointed out that $Me_3CC(O)OO\cdot$ would also be expected to be e reactive than alkylperoxyls for the same reason (see also: Zaikov, G. Howard, J. A.; Ingold, K. U. *Can. J. Chem.* **1969**, *47*, 3017–3029). The EPR method is therefore subject to an additional uncertainty.

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in the conventional manner to show a direct hydrogen atom transfer from the phenol to the peroxyl radical. Substantial deuterium kinetic isotope effects in phenol-inhibited autoxidations in nonpolar media[3-6] serve to confirm the direct H atom transfer for phenols having reactivities less than or equal to that of α-tocopherol. However, for phenols that are more reactive than α-T (for α-T we find $k_1^H/k_1^D = 5.4 \pm 0.4$) there is the possibility that reaction occurs via an initial, rate-controlling electron transfer,[29] in which case there would be no deuterium isotope effect.

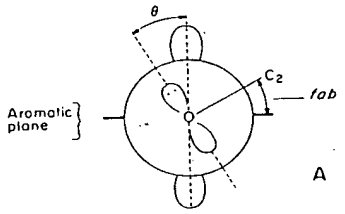
$$ROO\cdot + ArOH \xrightarrow[\text{controlling}]{\text{rate}} ROO^- + ArOH^+\cdot \qquad (6)$$

$$ArOH^+\cdot \rightarrow ArO\cdot + H^+ \xrightarrow{ROO^-} ROOH \qquad (7)$$

We therefore employed the IAS method to measure the deuterium isotope effect for the two most reactive phenols, IIIa ($k_1^H/k_1^D = 4.6 \pm 0.6$) and IIIb ($k_1^H/k^D = 4.4 \pm 0.4$). Since these two compounds exhibited a substantial isotope effect we conclude that H atom transfer is rate controlling in all cases.

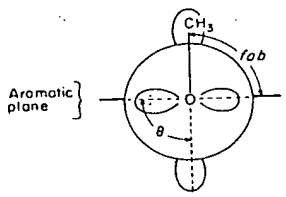
Structures and Stereoelectronic Factors. X-ray Crystallography. The k_1 value for α-T is about eight times larger than that for 4-methoxytetramethylphenol[3] (VIc), which could serve as a model for α-T except that it lacks the fused heterocyclic ring. As was noted in the introduction, we have attributed the high reactivity of α-T to the fact that the 2p-type lone pair of electrons on the ring oxygen is constrained by the heterocyclic ring to lie approximately perpendicular to the aromatic plane. It is therefore well positioned to stabilize the incipient α-tocopheroxyl radical; this weakens the O–H bond and, in consequence, α-T has a high k_1 value. By contrast, in VIc the steric interaction between the methoxy group and the methyl groups in the 3 and 5 positions forces the methoxy group into a position perpendicular to the aromatic plane. In this position the 2p-type lone pair on the methoxyl oxygen lies in the plane of the ring. It is therefore unable to stabilize the incipient phenoxyl radical. As a consequence, VIc has a relatively strong O–H bond and a relatively small k_1 value.

These conclusions were confirmed by X-ray crystallographic analyses of the pentamethyl-6-hydroxychroman, Ib (α-T is a liquid at room temperature), and of VIc.[3a] The X-ray structure of Ib showed that the heterocyclic ring adopted a half-chair conformation with a dihedral angle *fab* (see footnote to Table II) between the aromatic ring and the O–C_2 bond of 15.9° or 19.0°.[30] This implies that the 1-oxygen's 2p-type lone pair makes a dihedral angle, θ (≡*fab*), of about 17° with respect to the axis of the 2p orbital at the adjacent aromatic carbon, see A. The analysis of



A

VIc showed that the methoxyl group was almost perpendicular to the ring (*fab* = 88.6°).[3a] In this molecule, therefore, θ is presumably ca. 90°, see B.



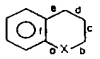
B

As an aid to understanding the relative magnitudes of the k_1 values found for different phenols, we undertook some additional X-ray analyses. In Table II we present torsion angles for the heterocyclic ring of Ib, Ic, IIb, IIId, and V. The complete X-ray structural data for Ic, IIb, IIId, and V are given as Supplementary Material; the data for Ib and VIc have been presented previously.[3a] Unfortunately, crystals suitable for X-ray analyses could not be grown for IIIa–c, nor for IVc and some other kinetically interesting phenols.

Table II. Summary of Torsion Angles (deg) for the Heterocyclic Ring of Various Hydroxychromans and Analogues as Determined by X-ray Diffraction Analysis[a]

angle	Ib[b]	Ib[c]	Ic[d]	Ic[e]	IIb	IIId	V
fab = θ	−15.9	−19.0	−13.7	−15.4	−37.8	−5.9	−10.8
abc	48.3	50.0	43.4	44.1	50.8	10.7	45.3
bcd	−62.7	−62.1	−60.1	−59.7	−33.3	−11.1	−67.7
cde	44.2	42.8	46.5	45.3	1.4		45.5
def (*cdf*) = γ	−11.2	−11.5	−17.1	−17.1	−15.6	(8.1)	−5.3
efa (*dfa*)	3.9	1.4	−0.3	1.2	3.0	(−1.8)	6.9

[a] Ring parameter designations are



for structures I, II, and V;

for structure III. [b] Molecule 1 of unit cell (ref 3a). [c] Molecule 2 of unit cell (ref 3a). [d] Triclinic crystal form. [e] Monoclinic crystal form.

EPR Spectroscopic Properties of Phenoxyls. The conformation that the fused heterocyclic ring adopts in a crystal of the phenol is not necessarily the same as that it adopts when the phenol is in solution. Some information regarding the solution conformation of the corresponding phenoxyl radical can be gained by EPR spectroscopy. Of greater importance is the fact that a detailed consideration of the magnitude of the hyperfine splittings (hfs) found for each phenoxyl radical provides valuable information about the extent to which the unpaired electron is delocalized in the radical. This is particularly useful because electron delocalization is expected to correlate with antioxidant activity. That is, the greater the electron delocalization the more stabilized will be the phenoxyl radical relative to the parent phenol and, hence, the weaker will be the O–H bond in the phenol and the greater will be k_1.

Most of the potentially interesting phenoxyl radicals were generated by UV photolysis of degassed solutions of the phenols in benzene/di-*tert*-butyl peroxide (5:1 (v/v)) at room temperature. Excellent spectra were generally obtained, and hyperfine splittings (hfs) were derived by comparison with computer-simulated spectra. These results are summarized in Table III.

Bimolecular Self-Reactions of Phenoxyls and the Phenoxyl–Oxygen Reaction. Under normal, in vitro, experimental conditions the phenoxyl radical produced in reaction 1 is destroyed by:

$$ROO\cdot + ArO\cdot \xrightarrow{\text{fast}} \text{nonradical products} \qquad (8)$$

Effective phenolic antioxidants yield phenoxyl radicals that are relatively unreactive toward one another and toward molecular oxygen.

$$ArO\cdot + ArO\cdot \xrightarrow{\text{slow}} \text{nonradical products} \qquad (9)$$

$$ArO\cdot + O_2 \xrightarrow{\text{slow}} \text{radical products} \qquad (10)$$

We have measured some rate constants for reaction 9 and have examined the effect of oxygen on the decay kinetics.[1e] These results are summarized in Table IV.

Discussion

The phenols listed in Table I show quite wide variations in their reactivities toward peroxyl radicals. The k_1 values obtained by the inhibited autoxidation of styrene method are more reliable, both in a relative and absolute sense, than those obtained by the laser-flash kinetic EPR method. This is particularly true for compounds having k_1 values greater than ca. 10^6 M^{-1} s^{-1}. The

(29) This may well be the reason that $Cl_3COO\cdot$ is so much more reactive toward α-T than are alkylperoxyls (see ref 14).

(30) There are two molecules of Ib which have slightly different structures in the unit cell (see Table II).

Table III. EPR Spectral Parameters for Some Phenoxyl Radicals[a]

parent phenol	g	a^H 2	4(CH_2)	5(CH_3)	7(CH_3)	8(CH_3)	a^{other}	ΔH_{pp}[b]
α-T[c]			1.47	5.98	4.57	0.94	0.098 (2 H)[d,e]	
Ia	2.00475	3.30 (1 H)	1.41	6.02	4.64	1.00		0.25
Ia[f]		3.22 (1 H)	1.40	6.00	4.62	1.00	0.09 (2 H)[d,g]	<0.1
Ib[c]			1.46	5.94	4.51	0.96	0.101 (2 H)[d,e]	
Ib	2.00476		1.48	6.04	4.55	0.96		0.3
Id	2.00475		1.55	6.35	4.72	1.06		0.3
If	2.00477		1.60	6.15	4.60	1.00		0.4
Ig	2.00472		1.45	6.00	4.56	0.96		0.3
Ij	2.00482		1.5 (1 H), 1.7 (1 H)	6.05	4.95	1.13		0.3
IVc	2.00431	(6.5 (1 H))	(0.7)	(4.45)	(4.45)	(0.7)	(4.4 (N))	0.35
V	2.00562	5.5 (1 H)		5.60	4.50	1.35		0.35

parent phenol	g	a^H 2	3(CH_2)	4(CH_3)	6(CH_3)	7(CH_3)	ΔH_{pp}[b]
IIIa	2.00468	1.98 (1 H)	0.28	5.80	4.75	1.10	0.2
IIIb	2.00471		*h*	5.78	4.78	1.03	0.2
IIIc	2.00462		*h*	6.00	4.95	1.11	0.5

parent phenol	g	a^H OCH_3	5	6	2	3	ΔH_{pp}[b]
MeOP[i]	2.005[j]	1.75	0.85 (1 H)	5.75 (1 H)	5.75 (1 H)	0.85 (1 H)	0.5
VIa	2.00482	1.50	0.95 (1 H)	5.43 (1 H)	5.43 (1 H)	0.95 (1 H)	0.2
VIb	2.00478	2.0	1.0 (1 H)	5.5 (CH_3)	4.5 (CH_3)	1.5 (CH_3)	0.2
VIc	2.00479	<0.1	1.56 (CH_3)	6.18 (CH_3)	6.18 (CH_3)	1.56 (CH_3)	0.3

[a] In benzene/di-*tert*-butyl peroxide (5:1 (v/v)) as solvent at room temperature unless otherwise noted. For numbering, see Table I. Hyperfine splittings and line widths are given in gauss. [b] Line width. [c] Data from ref 60. [d] Position 3. [e] These hdyrogens were not resolved by EPR but were shown by ENDOR to have equal hfs of about this magnitude. [f] In toluene/di-*tert*-butyl peroxide (5:1 (v/v)) at −15 °C. [g] See Figure 3, part C. [h] Not resolved. [i] 4-Methoxyphenol. [j] Spectrum changes rapidly with time so no attempt was made to obtain a precise *g* value.

Table IV. Rate Constants for the Bimolecular Self-Reactions of Some Phenoxyl Radicals in the Absence and Presence of Oxygen[a]

parent phenol	$2k_9$ (M^{-1} s^{-1}) O_2 absent[b]	O_2 present[c]
α-T	3×10^3	3×10^3
β-T	4×10^4	5×10^4
γ-T	4.5×10^4	
δ-T	1.5×10^5	2×10^5
DMT	4.5×10^3	
Ib	3×10^3	3×10^3
IIIa	4×10^3	
IVc	6×10^4	5×10^4
V	2×10^2	7×10^2

[a] Measured by kinetic EPR in benzene/di-*tert*-butyl peroxide (10:1 v/v)) at 23 °C at [ArOH] concentrations of 1, 5, and 50×10^{-3} M. See ref 1e.) [b] Sample degassed and sealed under vacuum. [c] O_2 saturated at 760 torr, $[O_2]$ = ca. 9.2×10^{-3} M (see text).

Table V. Dihedral *fab* Angles, k_1 Values and Calculated O-H Bond Strengths for Some Selected Phenols.

phenol	*fab*, deg	$10^4 k_1$, M^{-1} s^{-1}	D[ArO-H],[a] kcal/mol
α-T		320	80.4
Ib	17	380	80.2
IIa	38[b]	250	80.8
IIIb	6[c]	570	79.7
VIa	8[d,e]	94	82.1
VIb	8[d,e]	130	81.6
VIc	89[e]	39	83.2

[a] Calculated from data in ref 32. See text. [b] Angle for IIb. [c] Angle for IIId. [d] Assumed to be the same as for 4-methoxyphenol. [e] See ref 3.

ignificance of the LKEPR data is that they confirm, in a general way, the k_1 values obtained by the inhibited autoxidation procedure. Differences in individual k_1 values obtained by the two techniques should not be considered important.

Most of the differences in k_1 values between the various phenols we have studied can be attributed to the electronic effect of the group that is para to the hydroxyl function. Effects due both to conjugative electron donation and to inductive electron withdrawal can be identified, with the former being strongly dependent on the conformation of the para group with respect to the aromatic ring. Such an orientationally dependent contribution from electron delocalization to chemical reactivity is generally referred to as a stereoelectronic effect.[31]

The influence of structural changes on k_1 values will be given detailed consideration only for α-T and those other phenols that have two methyl groups ortho to the hydroxyl function. For the other phenols two comments will suffice: (1) α-T is more reactive than β-T, γ-T, and δ-T because these three tocopherols lack one or more ortho methyl groups and such electron-releasing groups stabilize phenoxyls and therefore increase k_1 values.[6] For the same reason IIIb is more reactive than IIId. (2) The 2,6-di-*tert*-butylphenols, VIIa–c, are less reactive than the corresponding 2,6-dimethylphenols, VIa,f,g, respectively, because the presence of two ortho *tert*-butyl groups in VII hinders the approach of the peroxyl radical.

Other, more subtle, structural changes are considered below under two main headings: (1) **Stereoelectronic Effects**—which are concerned with the orientation with respect to the aromatic plane of the p-type lone pair on the heteroatom para to the hydroxyl group; and (2) **Inductive Effects**—which are concerned with the inductive effect of groups attached to position 2 of those phenols that have a fused heterocyclic ring.

Stereoelectronic Effects. (i) General Comments. Differences in the reactivities of many of the para-RX-substituted phenols listed in Table I can be quite simply accounted for in terms of extent of overlap between the p-type orbital on X and the aromatic π-electron cloud or, more specifically, in terms of the dihedral angle between the aromatic ring and the R–X bond. This angle, which is designated by *fab* in structure A (see Results and Table II), has been obtained by X-ray analysis of a crystal of a suitable phenol. To a first approximation the *fab* angle can be assumed to equal the dihedral angle, θ, between the p-type lone pair on X and the axis of the p orbital at the adjacent aromatic carbon (see A) for the phenol dissolved in an organic solvent. Stabilization of the phenoxyl radical will be maximized, and hence k_1 will be optimized, when orbital overlap is minimized, i.e., when $\theta = 0°$.

(31) Deslongchamps, P. "Stereoelectronic Effects in Organic Chemistry"; Pergamon Press: Oxford, 1983. Kirby, A. J. "The Anomeric Effect and Related Stereoelectronic Effects at Oxygen"; Springer-Verlag: Berlin, 1983. Easton, C. *Sci. Prog., Oxf.* **1983**, *68*, 503–517.

Stabilization will be at a minimum when these two orbitals are orthogonal, i.e., when $\theta = 90°$.

The general phenomenon can be illustrated by comparing the *fab* angles listed in Table II with the k_1 values listed in Table I. This is done for the hydroxychroman Ib, the hydroxychromene IIa, the hydroxydihydrobenzofuran IIIb, 4-methoxy-2,6-dimethylphenol VIa, 4-methoxy-2,3,6-trimethylphenol VIb, and 4-methoxytetramethylphenol VIc in Table V. For the phenols having a fused oxygen-containing heterocyclic ring but otherwise rather similar structures, viz., IIa, Ib, and IIIb, reactivity increases from 250×10^4, to 380×10^4, to 570×10^4 M^{-1} s^{-1}, respectively, as *fab* decreases from 38°, to 17°, to 6°, respectively. Similarly, although k_1 increases from 94×10^4 to 130×10^4 M^{-1} s^{-1} on going from VIa to VIb because of the radical-stabilizing effect of the additional *m*-methyl group,[6] it decreases dramatically to 39×10^4 M^{-1} s^{-1} in VIc with the addition of the second *m*-methyl group. The first two of these phenols are presumed to have *fab* angles close to 8° (the value found for 4-methoxyphenol)[3] while for the last the *fab* angle is close to 90°. Thus, for structurally related phenols there is a striking correlation between *fab* dihedral angles and k_1 values both for those compounds that have a fused heterocyclic ring and for those that do not. (Although the dihedral angles in the crystal are not necessarily the same as the dihedral angles adopted by these phenols in solution (vide infra), there is no reason to expect that the relative order in which *fab* angles increase along a series of phenols will differ dramatically from the relative order in which θ values increase.) The correlation between *fab* angle and k_1 value therefore supports our contention that, for the phenolic antioxidants with which we are dealing, stabilization of the phenoxyl radical by the p-type lone pair on the para heteroatom, i.e., C ↔ D, is influenced by the orientation of this lone pair with respect to the aromatic plane. That is, the reactivities of these phenols are subject to stereoelectronic effects.

C D

(ii) ArO–H Bond Strengths and "Activation" by a "Perpendicular" OMe Group. The stabilization energy of a phenoxyl radical, ArO·, relative to that of C_6H_5O·, is given by the difference in the O–H bond strengths, $D[C_6H_5O–H] - D$[ArO–H]. Values of D[ArO–H] can be estimated from measured values for k_1 by using a correlation (eq I) that can be derived from work reported by Mahoney and DaRooge,[32] viz.

$$D[\text{ArO–H}]\ (\text{kcal/mol}) = 100.4\ (\pm 1.1) - 3.07\ (\pm 0.20) \log (k_1/M^{-1}\ s^{-1}) \quad (I)$$

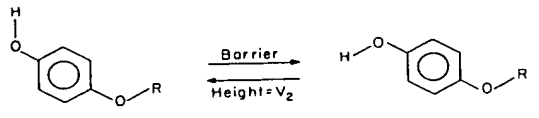
The k_1 values on which this relation is based were measured at 60 °C with peroxyl radicals derived from 9,10-dihydroanthracene.[32] Our own k_1 values have been used to derive the ArO–H bond strengths listed in Table V, no allowance having been made for the temperature difference (which would correspond to less than a factor of 2 in k_1 values) or for the type of peroxyl radical. However, it should be noted that implicit to eq I is the possibly unjustified (vide infra) assumption that the entropies of activation for reaction 1 are equal for all phenols. If we ignore this potential complication for the moment we see that, relative to 4-methoxytetramethylphenol (VIc, $\theta \sim 90°$), the phenoxyl radicals derived from IIa, α-T, Ib, and IIIb are stabilized by 2.4, 2.8, 3.0, and 3.5 kcal/mol, respectively.

It is instructive to compare these estimated O–H bond strengths with the results of Baird's[33] MNDO theoretical study of 1,4-dihydroxybenzene and the 4-hydroxphenoxyl radical. Values of $D[p\text{-}HOC_6H_4O–H]$ were calculated to be weaker than $D[C_6H_5O–H]$ by 3.8 kcal/mol when the para-O–H bond was coplanar with the ring (a value in good agreement with the 3.7 kcal/mol reported by Mahoney and DaRooge[32]) and 1.3 kcal/mol when the para O–H bond was twisted perpendicular to the ring. Our own data (Table V) imply that a change in *fab* from ca. 90° to nearly 0° decreases the ArO–H bond strength by ca. 3.5 kcal/mol rather than by the ca. 2.5 kcal/mol calculated by Baird. This difference could be due to the fact that the "effective" θ for VIc is significantly less than the measured *fab* angle. That is, H atom abstraction from VIc will become easier the further the OMe group twists from its equilibrium position perpendicular to the aromatic plane. Since there will certainly be some libration of the OMe group about the C_4–OMe bond, the "effective" value of θ may well be considerably less than 90°. This would reduce the activation energy for the reaction. However, it seems probably that this rate-accelerating effect (relative to a "fixed" $\theta = 90°$) would be more than compensated by a reduced Arrhenius pre-exponential factor, i.e., the rate-accelerating effect of the decreased enthalpy of activation would be outweighed by the rate-retarding effect of the increased entropy of activation. It is, of course, unlikely that there would be any significant changes in "effective" θ values for those phenols which have a fused heterocyclic ring.

Baird[33] has pointed out that the residual stabilization of 1.3 kcal/mol in the 90° twisted p-HOC_6H_4OH structure is due mainly to delocalization into the ring's π-electron system in the radical from the other lone pair of the twisted OH group. That there is some stabilization of 4-methoxytetramethylphenoxyl relative to 2,3,5,6-tetramethylphenoxyl is clear from the k_1 values for VIc (3.9×10^5 M^{-1} s^{-1}) and VIg (7.5×10^4 M^{-1} s^{-1}). In fact, the "perpendicular" 4-OMe group in VIc appears to be about as activating as the 4-Me group in pentamethylphenol, VId ($k_1 = 3.6 \times 10^5$ M^{-1} s^{-1}). This result contradicts the general belief[34] that a "perpendicular" alkoxy group will be "deactivating" relative to both a methyl group and a hydrogen atom. That is, an alkoxy group is electron releasing by a resonance, or $+M$, effect (because of its p-type lone pair of electrons), but it is also electron withdrawing because of its inductive, or $-I$, effect (which arises because oxygen is more electronegative than carbon or hydrogen). If an alkoxy group is attached to an aromatic ring, is coplanar with the ring, and is "activating" relative to an alkyl group or a hydrogen atom in some physical process or chemical reaction, then it has generally been assumed that a perpendicular alkoxy would be "deactivating", i.e., the $+M$ activating effect would be inoperative in the perpendicular conformation and the influence of the alkoxy group would be manifest only by its $-I$ effect. From our results it is clear that the $-I$ effect of a perpendicular alkoxy group is more than outweighted by a residual $+M$ effect which we attribute to a resonance contribution from the other lone pair on the oxygen.

(iii) Dependence of ArO–H Bond Strengths, OH Rotational Barriers, and k_1 Values on θ. Because there is conjugative participation in the stabilization of 4-alkoxyphenoxyl radicals by two inequivalent oxygen lone pairs, the potential function for rotation is rather complicated.[33] For $\theta < 40°$ Baird's results indicate that the energy loss due to twisting is approximately proportional to $1 - \cos\theta$, and the change in $D[p\text{-}HOC_6H_4O–H]$ is $\approx 3.2(1 - \cos\theta)$ kcal/mol.[33] However, the estimated O–H bond strengths for tetraalkylated 4-alkoxyphenols of known *fab* angle (i.e., Ib, IIa, IIIb, and VIc from Table V) do not discriminate between this relation and the more conventional[1c,1d] representation of p-orbital overlap in terms of $\cos^2\theta$ (see Figure 1).

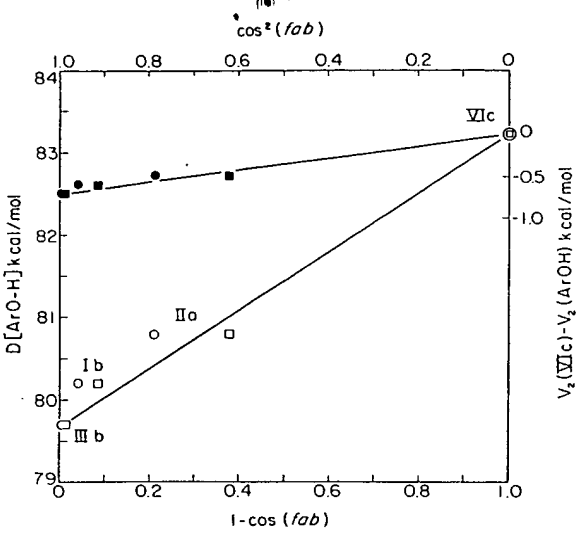
We have also found[35] that for a number of our phenols the potential barriers to rotation of the OH group, V_2 (see E ⇄ F), do not serve to discriminate between a $1 - \cos\theta$ and a $\cos^2\theta$ law (see also Figure 1). These OH rotational barriers, which were



E F

obtained by measuring low-temperature dielectric relaxation rates,

(32) Mahoney, L. R.; DaRooge, M. A. *J. Am. Chem. Soc.* **1975**, *97*, 4722–4731.
(33) Baird, N. C. *Tetrahedron* **1984**, *40*, 3383–3385.
(34) Taft, R. W. Jr.; Evans, H. D. *J. Chem. Phys.* **1957**, *27*, 1427–1428.



ıre 1. Open points: phenolic bond strengths, D[ArO–H], calculated ı eq I plotted against 1 − cos (*fab*) (○) and against cos² (*fab*) (□). :d points: barriers to rotation of the phenolic OH group, V_2, relative ıe barrier in VIc plotted against 1 − cos (*fab*) (●) and against cos²) (■). For the meaning of identifying symbols, see Table I.

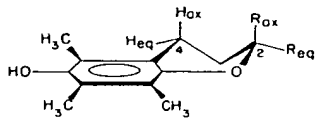
indicate that a perpendicular alkoxy group is about as acting relative to hydrogen as is a methyl group.[35]

is interesting to note that V_2 was found[35] to decrease by ca. kcal/mol[36] on going from VIc ($\theta \sim 90°$, $V_2 \sim 2.4$–3.0 /mol[36]) to IIIb ($\theta \sim 6°$), see Figure 1. A 4-alkoxy substituent ch is coplanar with the aromatic ring therefore causes the gy difference between a conformation with a coplanar OH ıp (i.e., the ground state of the phenol) and a conformation ı a perpendicular OH group to be 0.68 kcal/mol smaller than energy difference between these conformations when the koxy group is perpendicular to the ring. Abstraction of the ıolic hydrogen will occur with the OH group perpendicular ıe aromatic ring in order to gain resonance stabilization by calization of the developing unpaired electron into the aromatic stem. Because of this difference in the energies of the ground I planar) and twisted (OH perpendicular) states of the two ıols, the enthalpy for H abstraction from IIIb will be 0.68 /mol less than that for H abstraction from VIc. The actual :rence in $\Delta G_1^{\ddagger}$ between IIIb and VIc favors H abstraction ı IIIb by nearly one additional kcal/mol, i.e., $\Delta G_1^{\ddagger}$(IIIb) − ‡(VIc) = $-RT$ ln (573/39) = 1.6 kcal/mol. In summary, efore, a phenol with a coplanar *p*-alkoxy group has enhanced)xidant activity relative to a phenol with a perpendicular alkoxy p for two reasons. First, the coplanar alkoxy group reduces :nergy, V_2, required to twist the OH group from its preferred ınar position (see E ⇄ F) to a perpendicular position by ~0.7 /mol. Second, the coplanar alkoxy group stabilizes the sition state for reaction by increasing the delocalization of ınpaired electron in the developing phenoxyl radical (see C)), producing an additional diminution of $\Delta G_1^{\ddagger}$ of ~0.9 /mol.

v) The Hypothetical "Planar" 4-Methoxytetramethylphenol. ıld such a species be as good an antioxidant as a phenol such Ib in which (virtual) coplanarity is enforced by the hetero- c ring? In an attempt to answer this question, we examine the enhancement in k_1 produced by an additional, but non- :ring, *m*-methyl group. The ratio of k_1 values for the following ol pairs are as follows: α-T/DMT, 1.79; VIb/VIa, 1.38; 'VIe, 3.27; VIe/VIf, 1.29; and $^1/_2$VIg/VIh = $^1/_2$3 = 1.5. e 4-methoxy-2,3,6-trimethylphenol, VIb, has a k_1 value of < 10^6 M^{-1} s^{-1} and IIIb has a k_1 value of 5.7 × 10^6 M^{-1} s^{-1}, the enhancement in k_1 produced by ring closure and the consequent addition of a *m*-alkyl group amounts to a factor of 5.7/1.3 = 4.4. This is considerably larger than any of the above-listed *m*-methyl group-enhancement factors. We therefore conclude that the heterocyclic ring provides a more efficient antioxidant than would a hypothetical "planar" 4-alkoxytetramethylphenol. We presume that the origin of this heterocyclic ring effect lies in entropic factors.[37] That is, it is necessary to "freeze-out" the libration of the 4-OMe group about the C_4–O bond in the transition state for H abstraction from VIb but not from IIIb. This means that the bond strengths calculated from eq I for phenols having a fused heterocyclic ring (Table V and Figure 1) are probably smaller than their true values. The difference in D[ArO–H] between VIc and IIIb will therefore be less than the calculated 3.5 kcal/mol and so would be in better agreement with Baird's[33] calculations (vide supra).

It should perhaps be emphasized that the foregoing discussions assume that the mechanism of reaction 1 remains the same for all the phenols examined in this work. That this is the case is implied by the fact that phenols having quite widely different k_1 values all exhibit substantial deuterium kinetic isotope effects (see Results).

(v) "Puckering" of the Heterocyclic Ring and Effect of Different Heteroatoms. The heterocyclic ring in the hydroxychromans has a half-chair conformation in the crystal with the extent of ring puckering being to some extent limited by a 1,3 steric interaction between the pseudoaxial hydrogen at the 4-position, H_{ax}, and the pseudoaxial substituent at the 2 position, R_{ax}, see G. Replacing



G

both 2-CH_3 groups in Ib by hydrogen to form Ia will permit ring puckering to increase. As a consequence, θ will increase and so k_1 will decrease, as is observed (see Table I). Similarly, in the replacement of one of the 2-CH_3 groups in Ib by the bulky phytyl group to form α-T the remaining methyl group (which is expected to reside in the axial position) will probably be pushed closer to H_{ax}. That is, θ is expected to be larger in α-T than in Ib and k_1 to be smaller, as is observed. (The lower reactivities of Ic–j relative to **Ib** we attributed *mainly* to polar factors, vide infra).

Some puckering of the heterocyclic ring in IIIa induced by a 1,2 steric interaction between the CH_3 group in position 2 and the eclipsed H in position 3 may be the reason that IIIa is somewhat less reactive than IIIb.

An unfavorable conformation of the heterocyclic ring in IVc also provides a simple explanation for the relatively low reactivity of this compound. That is, we had expected that IVc would be a better antioxidant than Ia because nitrogen, being less electronegative than oxygen, would be better able to stabilize a neighboring radical center by conjugative delocalization of its lone pair of electrons.[38] However, an inspection of space-filling models indicated that there would be very severe steric interactions between an equatorial *N*-ethyl group and the methyl group at position 8 on the aromatic ring. As a consequence, we presume[39] that the *N*-ethyl group adopts the axial position, as in H, with the nitrogen lone pair lying rather close to the plane of the aromatic ring, i.e., in a relatively unfavorable position to stabilize the incipient phenoxyl radical.

It is obvious that the steric interaction present in IVc (and IVb)[40] would be much less with the ethyl group replaced by a

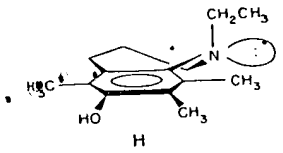
5) Gilchrist, J. le G.; Burton, G. W.; Ingold, K. U. *Chem. Phys.* **1985**, 73–481.

5) Differences in V_2 between phenols have been determined with much precision than the absolute value of V_2 for any of the phenols men- l.[35]

(37) We tend to rule out a Mills-Nixon effect as the origin of the enhanced activity of the phenols having a fused heterocyclic ring, see: Mitchell, R. H.; Slowey, P. D.; Kamada, T.; Williams, R. W.; Garratt, P. J. *J. Am. Chem. Soc.* **1984**, *106*, 2431–2432. For a contrary view, see: Hiberty, P. C.; Ohanessian, G.; Delbecq, F. *J. Am. Chem. Soc.* **1985**, *107*, 3095–3100.

(38) See e.g.: Burkey, T. J.; Castelhano, A. L.; Griller, D.; Lossing, F. P. *J. Am. Chem. Soc.* **1983**, *105*, 4701–4703.

(39) Crystals suitable for X-ray analysis could not be obtained.



H

hydrogen atom, i.e., IVa. However, this compound was found to be unstable in air even in the crystalline state. It was not, therefore, used as an antioxidant though it must be fairly reactive toward peroxyl radicals since they should be able to abstract hydrogen from either heteroatom.[41] The low reactivity of IVb can be attributed to polar factors (vide infra).

The formation of V by reaction of 4-mercapto-2,3,6-trimethylphenol with 3-methyl-2-buten-1-ol following the general procedure used to prepare Ib from trimethylhydroquinone was somewhat unexpected because similar routes have been used to prepare purported sulfur analogues of α-T.[42,43] There can be no doubt regarding the structure of V, since it was confirmed by X-ray analysis. We consider it probable that if hydroxydihydrothiobenzopyrans have been made by others[42,43] they will also have the two alkyl groups that are attached to the heterocyclic ring, joined to the 4-position and not to the 2-position as claimed. It is probably inappropriate to compare the reactivity of V with that of any other compound listed in Table I both because of its different structure and because the stoichiometric factor for V was only ca. 1.5 rather than ca. 2.0 as found for all other compounds in this table.[44] Nevertheless, it is worth noting that sulfur is generally considered to be more effective than oxygen at stabilizing a neighboring radical center[46] and that the relatively small *fab* angle in V (see Table II) is consistent with a relatively large value for k_1.[47]

Inductive Effects. A number of food preservation tests have shown that Ic is superior to α-T as an antioxidant.[49-52] Since Ic is less reactive toward peroxyl radicals than α-T in homogeneous nonpolar solvents (see Table I), its effectiveness in food preservation must have some other origin. Similarly, Id and Ie were less effective food preservatives than Ic,[49] although both compounds are more reactive toward peroxyl radicals.

The decreased reactivity of Ic–f and Ii and Ij, relative to Ib, we attribute *principally* to the electron-withdrawing nature of the various R_2 groups. The inductive,[53,54] or field,[55] effect of these electron-withdrawing groups will impair the ability of the 2p-type lone pair on the ring oxygen to participate in the stabilization of the phenoxyl radical. That is, an electron-withdrawing substituent in the neighborhood of the heteroatom could reduce k_1 even if the dihedral angle, θ, between the axis of the 2p-type lone pair and the axis of the p orbital at the adjacent aromatic carbon remains the same (as appears to be roughly the case for Ib and Ic, see *fab* angles given in Table II). In solution the value of θ may vary somewhat with substituent. For this reason, the correlation shown in Figure 2 between the log $(k_1/M^{-1}\ s^{-1})$ values for all the phenols from class I that have $R_1 = CH_3$ and the σ_I substituent constants[54] of their respective R_2 group is considerably better than might reasonably have been expected. The line drawn in this figure (which ignores the point for Ic) has a slope $\rho = -1.25$. It would appear that when a carboxylic acid group is close to the oxygen atom in the heterocyclic ring that it may have a specific deactivating effect, possibly associated with hydrogen bonding, since the σ_I value for C(O)OH (0.30) is actually less than that for C(O)OMe (0.32)[54,56] (cf. also Ie vs. If).

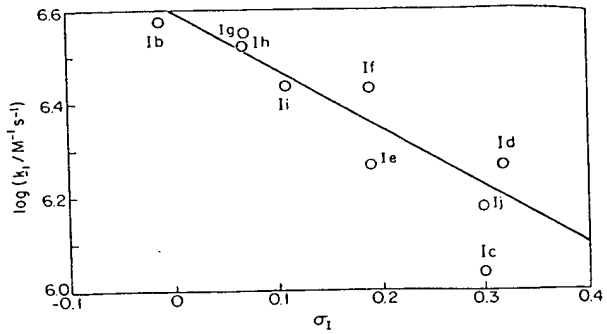


Figure 2. Plot of log $(k_1/M^{-1}\ s^{-1})$ for phenols from class I having $R_1 = CH_3$ vs. the σ_I values for their respective R_2 substituents. The σ_I values are from ref 54. Since σ_I values were not available for the R_2 substituents of Ie and Ig, these values have been assumed to be the same as those for the corresponding ester groups (If and Ih, respectively). For the meaning of identifying symbols, see Table I.

The differences in reactivity between IIa and IIb and between IIIb and IIIc can also be attributed to the inductive effect of the carboxylate group. The magnitude of this effect decreases, and hence k_1 increases, the further the carboxylate group is from C_2, cf. Ic vs. Ie vs. Ig, and Id vs. If vs. Ih. The very low reactivity of the amide IVb compared with the amine IVc can also be attributed to the polar effect of the acetyl group ($\sigma_I = 0.30$).[54] In this case, the electron-withdrawing substituent is directly attached to the heteroatom and so the effect is particularly dramatic.

Inductive effects may also explain the exceptional food-preserving properties of Ic.[58] This is because the CO_2H group will be ionized at the pH of most food products that contain moisture and the CO_2^- group is, inductively, quite strongly electron releasing ($\sigma_I = -0.19$,[54] $F = -0.27$[55a]).

(40) Svensson, K. G.; Nilsson, J. L. G. *Acta Pharm. Suec.* **1973**, *10*, 277–284.

(41) 6-Ethoxy-2,2,4-trimethyl-1,2-dihydroquinoline (ethoxyquin) and related compounds are known to be excellent antioxidants at temperatures below 100 °C. See e.g.: Nekipelova, T. D.; Gagarina, A. B. *Dokl. Akad. Nauk SSSR* **1976**, *226*, 626–629. Nekipelova, T. D.; Gagarina, A. B.; Emanuel, N. M. *Ibid.* **1978**, *238*, 392–395. Lobanova, T. V.; Kasaikina, O. T.; Ivanov, Yu. A.; Shapiro, A. B.; Gagarina, A. B. *Ibid.* **1979**, *245*, 643–646. Kasaikina, O. T.; Kartasheva, Z. S.; Lobanova, T. V.; Rusina, I. F.; Ivanov, Yu. A.; Gagarina, A. B. *Neftkhimiya* **1982**, *22*, 265–271. Kasaikina, O. T.; Lobanova, T. V.; Fentsov, D. V.; Ivanov, Yu. A. *Izv. Akad. Nauk SSSR Ser. Khim.* **1983**, 2214–2218. Kasaikina, O. T.; Lobanova, T. V.; Fentsov, D. V. *Ibid.* **1983**, 2219–2223.

(42) Karrer, P.; Leiser, P. *Helv. Chim. Acta* **1944**, *27*, 678–684.

(43) Valashek, I. E.; Shakhova, M. K.; Samokhvalov, G. I. *Zh. Org. Chim.* **1982**, *18*, 2497–2500.

(44) Unusual stoichiometric factors have been reported for other sulfur-containing chain-breaking antioxidants.[45]

(45) Gardner, D. V.; Howard, J. A.; Ingold, K. U. *Can. J. Chem.* **1964**, *42*, 2847–2851.

(46) See e.g.: Biddles, I.; Hudson, A.; Whiffen, J. T. *Tetrahedron* **1972**, *28*, 867–874. Wayner, D. D. M.; Arnold, D. R. *Can. J. Chem.* **1984**, *62*, 1164–1168. Nonhebel, D. C.; Walton, J. C. *J. Chem. Soc., Chem. Commun.* **1984**, 731–732. Griller, D.; Nonhebel, D. C.; Walton, J. C. *J. Chem. Soc., Perkin Trans. 2* **1984**, 1817–1821. Luedtke, A. E.; Timberlake, J. W. *J. Org. Chem.* **1985**, *50*, 268–270.

(47) The value of k_1 was obtained by means of an equation that avoids the requirements to know the stoichiometric factor.[3b,48]

(48) Tsepalov, V. F.; Kharitonova, A. A.; Gladyshev, G. P.; Emanuel, N. M. *Kinet. Katal.* **1977**, *18*, 1261–1267. Kharitonova, A. A.; Kozlova, Z. G.; Tsepalov, V. F.; Gladyshev, G. P. *Ibid.* **1979**, *20*, 593–599.

(49) Scott, J. W.; Cort, W. M.; Harley, H.; Parrish, D. R.; Saucy, G. *J. Am. Oil Chem. Soc.* **1974**, *51*, 200–203.

(50) Cort, W. M.; Scott, J. W.; Arauj, M.; Mergens, W. J.; Cannalonga, M. A.; Osadca, M.; Harley, H.; Parrish, D. R.; Pool. W. R. *J. Am. Oil Chem. Soc.* **1975**, *52*, 174–178.

(51) Cort, W. M.; Scott, J. W.; Harley, J. H. *Food Tech. (Chicago)* **1975**, *29*, 46–50.

(52) Scott, J. W.; Cort, W. M. *Cosmet. Toiletries* **1976**, *91*, 39–44.

(53) Exner, O. In "Advances in Linear Free Energy Relationships"; Chapman, N. B., Shorter, J. S., Eds.; Plenum Press: New York, 1972; Chapter 1.

(54) Charton, M. *Prog. Phys. Org. Chem.* **1981**, *13*, 119–251.

(55) (a) Swain, C. G.; Unger, S. H.; Rosenquist, N. R.; Swain, M. S. *J. Am. Chem. Soc.* **1983**, *105*, 492–502. (b) For some critical comments on this paper see: Reynolds, W. F.; Topsom, R. D. *J. Org. Chem.* **1984**, *49*, 1989–1992. Hoefnagel, A. J.; Oosterbeek, W.; Wepster, B. M. *Ibid.* **1984**, *49*, 1993–1997. Charton, M. *Ibid.* **1984**, *49*, 1997–2001. Swain, C. G. *Ibid.* **1984**, *49*, 2005–2010. Marriott, S.; Reynolds, W. F., Topsom, R. D. *Ibid.* **1985**, *50*, 741–743.

(56) Swain's[55a] F values show a similar difference, viz., F(C(O)OH) = 0.44, F(C(O)OR) = 0.47, but Inamoto's[57] ι values are identical for these two substituents.

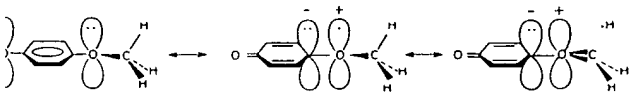
(57) Inamoto, N.; Masuda, S. *Chem. Lett.* **1982**, 1007–1010.

(58) Of course, other properties unique to Ic may also be involved in food preservation such as its greater mobility between aqueous and lipid regions in the food compared to α-T,[59] or its presumed ability to chelate catalytic metal ions.

(59) Doba, T.; Burton, G. W.; Ingold, K. U. *Biochem. Biophys. Acta* **1985**, *835*, 298–303. Niki, E.; Kawakami, A.; Saito, M.; Yamamoto, Y.; Tsuchiya, J.; Kamiya, Y. *J. Biol. Chem.* **1985**, *260*, 2191–2196.

EPR Spectroscopic Evidence Regarding the Structure and abilization of Phenoxyl Radicals. The hfs assignments for the romanoxyls that are given in Table III are based on those of ukai et al.[60] for the radicals derived from α-T and Ib which are so given in this table. The hfs for the phenoxyls derived from e dihydrobenzofurans IIIa–c, the dihydrobenzothiopyran V, and methoxytrimethylphenol VIb were assigned by analogy. Hfs signments for the phenoxyls from 4-methoxyphenol and its 5-dimethyl (VIa) and tetramethyl (VIc) substituted derivatives e obvious. Although a reasonably good fit between measured d simulated spectra was obtained for the radical derived from e tetrahydroquinoline IVc by using the listed hfs, these numbers ve been placed in parentheses because the fit is unlikely to be ique. That is, it is highly improbable that the H hfs for the and 7-CH_3 groups, the N atom, and the CH_2 of the ethyl group ould all be accidentally equivalent. A proper assignment of hfs r this radical would have required a number of specifically uterated compounds. However, the benefit that would have en gained from this information did not, in our view, justify ch a massive synthetic effort. Finally, under these conditions ectra too weak to allow firm hfs assignments to be made were tained from Ic and the chromenoxyl derived from IIa.

An interesting conformational effect can be observed in the EPR ectra of the phenoxyl radicals derived from 4-methoxyphenol d its methylated derivatives, VIa–c.[61] For those radicals which ve at least one non-methylated meta position, hfs by the me- oxyl group's hydrogens are readily observed ($a^H(OCH_3)$ = 5–2.0 G). Spin reaches these H atoms by hyperconjucation via 2p-type lone pair on the methoxyl oxygen, I ↔ J ↔ K. In



I J K

c steric interactions between the two *m*-methyl groups and the thoxy group force the latter into a position perpendicular to aromatic ring (*fab* = 88.6°). For this reason, little or no spin ches the 2p lone pair and so none can reach the H atoms of s methoxyl group ($a^H(OCH_3)$ < 0.1 G). One natural, but eresting, consequence is that the spin must remain on the enoxyl oxygen *and* on the aromatic ring. There is, therefore, re spin density on the aromatic ring, and this spin density centrates itself on the aromatic carbon atoms at the ortho itions (where it is "visible") and at the para position (where s "invisible"). Spin density at the ortho aromatic carbon atoms lirectly monitored by the hfs of the H atoms of the *o*-methyl ups. The "visible" increase in spin density at this position in manifests itself, therefore, as a significant increase in $a^H(o\text{-}CH_3)$ in the phenoxyl derived from this radical (6.18 G) compared h the values in the radicals from VIa (5.43 G) and VIb (4.50 1 5.50 G).

t is interesting to note that the orientation of the methoxyl up with respect to the aromatic plane has no effect on the *g* ues of this series of phenoxyls. This would certainly not be case for 4-XCH_3-substituted phenoxyls in which X came from second (e.g., sulfur[62,63]) or third row (e.g., selenium[64,65]) of periodic table and so had a higher spin–orbit coupling constant n oxygen. In fact, the only phenoxyl *g* values to differ sig-

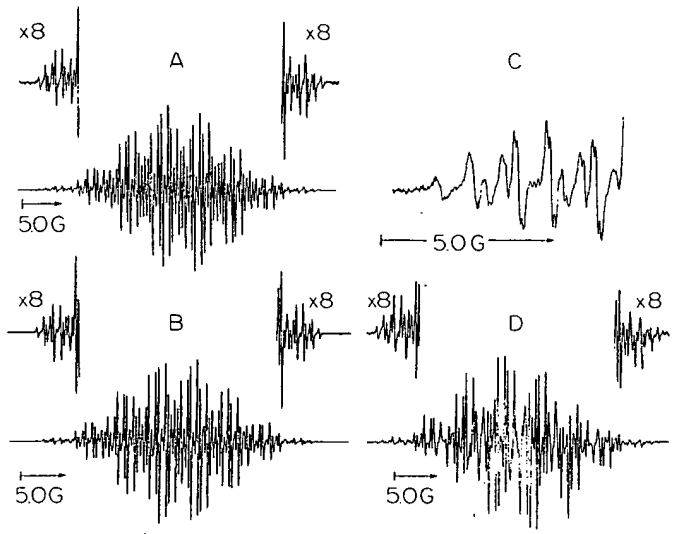


Figure 3. EPR spectrum of phenoxyl radical formed from Ia in toluene/di-*tert*-butyl peroxide (5:1 (v/v)): (A) measured at −15 °C and a modulation amplitude of 0.1 G; (B) computer simulation of A with use of the hyperfine splitting values given in Table III; (C) amplified and expanded low-field wing of the spectrum recorded at −15 °C and a modulation amplitude of 0.02 G; (D) measured at room temperature and a modulation amplitude of 0.1 G. The total spectral width in D is 0.25 G larger than in A and some distortion of the signal is apparent. The high- and low-field wings of the A, B, and D spectra are also shown at 8 times the gain of the central spectrum.

nificantly from the 2.0046–2.0048 found for radicals having an oxygen atom para to the phenoxyl oxygen are those for the radicals with a nitrogen atom (IVc, 2.0043) and with a sulfur atom (V, 2.0056) in this position.[66]

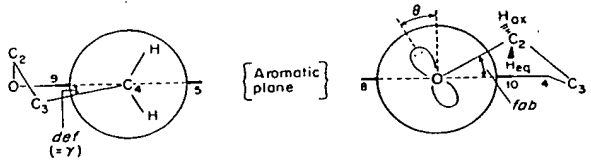
The chromanoxyl radicals, including α-tocopheroxyl, have interesting EPR spectra.[1d,60,67] The two H atoms on C-4 are magnetically equivalent for all but one of these radicals. The exceptional radical is that formed from Ij. This radical is unique in having a heteroatom directly bonded to C-2. In terms of structure G, it seems likely that Ij has $R_{ax} = OCH_3$ and $R_{eq} = CH_3$ since this will miminize the 1,3 steric interaction between the groups attached to C-2 and the pseudoaxial hydrogen on C-4. The magnetic inequivalence of H_{ax} and H_{eq} may be due to a greatly enhanced puckering of the heterocyclic ring (relative to Ib) which could explain why Ij is less reactive than Id (see Figure 2). Alternatively, there may be some specific interaction between H_{ax} and the oxygen atom of the methoxyl group.

The fact that the two H atoms on C-4 are magnetically equivalent has previously been specifically pointed out by Mukai et al.[60] for α-T and Ib. In addition, these workers showed by ENDOR that the two H atoms on C-3 (which they could not resolve by EPR, though we have achieved a partial resolution for the radical from Ia, vide infra) are also equivalent.[60] On this basis, they suggested that the heterocyclic ring was coplanar with the aromatic ring. This is, of course, inconsistent with our X-ray structures for Ib and Ic which show that the dihedral angles, *def*,

60) Mukai, K.; Tsuzuki, N.; Ishizu, K.; Ouchi, S.; Fukuzawa, K. *Chem. s. Lipids* **1981**, *29*, 129–135.
61) Our values for the EPR spectral parameters for the phenoxyls derived 1 4-methoxyphenyl, VIa, and VIc are in satisfactory agreement with those rted by other workers, see: Uber, W.; Stegman, H. B. In "Landolt-nstein, New Series, Magnetic Properties of Free Radicals"; Fischer, H., wege, K.-H., Eds.; Springer-Verlag: Berlin, 1979; Vol. 9, Chapter 8, Part pp 29–214.
62) Gilbert, B. C.; Larkin, J. P.; Norman, R. O. C. *J. Chem. Soc., Perkin ns. 2* **1973**, 272–277.
63) Scaiano, J. C.; Ingold, K. U. *J. Am. Chem. Soc.* **1976**, *98*, 4727–4732.
64) Scaiano, J. C.; Ingold, K. U. *J. Phys. Chem.* **1976**, *80*, 1901–1908.
65) Scaiano, J. C.; Ingold, K. U. *J. Am. Chem. Soc.* **1977**, *99*, 2079–2084.

(66) Nitrogen and sulfur have respectively smaller and larger spin–orbit coupling constants than oxygen, see: Morton, J. R.; Rowlands, J. R.; Wiffen, D. H. National Physical Laboratory (U.K.), Publ. BPR 13, 1962.
(67) For other EPR spectroscopic studies of α-tocopheroxyl and related radicals which postdate the corrected hfs assignments given in ref 60, see: Mukai, K.; Tsuzuki, N.; Ouchi, S.; Fukuzawa, K. *Chem. Phys. Lipids* **1982**, *30*, 337–345. Matsuo, M.; Matsumoto, S. *Lipids* **1983**, *18*, 81–86. Mukai, K.; Morimoto, C.; Ishizu, K. *Tetrahedron Lett.* **1983**, *24*, 5099–5102. Matsuo, M.; Matsumoto, S.; Ozawa, T. *Org. Mag. Reson.* **1983**, *21*, 261–264. Tsuchiya, J.; Niki, E.; Kamiya, Y. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 229–232. Bascetta, E.; Gunstone, F. G.; Walton, J. C. *Chem. Phys. Lipids* **1983**, *33*, 207–210. Mukai, K.; Takamatsu, K.; Ishizu, K. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 3507–3510. Eloranta, J.; Hämäläinen, E.; Salo, E.; Mäkelä, R.; Kekäläinen, U. *Acta Chem. Scand. A* **1983**, *A37*, 383–391. Note that in the last mentioned reference (which deals in part with solvent effects on the hfs of α-tocopheroxyl) the assignments of hfs to the 5 CH_3 and 7 CH_3 groups are incorrect.

between the C_3–C_4 bond and the aromatic ring are ca. 11° and ca. 17°, respectively (see Table II and structure L). That is, in magnitude the *def* angles are comparable to the *fab* angles (i.e., γ is comparable to θ; see L and M). The EPR data for the chromanoxyl radicals and the X-ray data for the chroman molecule would, of course, be consistent if, in solution, the half-chair to half-chair interconversion of the heterocyclic ring was rapid (on the EPR time scale). This seems possible for the radical derived from Ib and for related 2,2-disubstituted 5,7,8-trimethylchromanoxyls since Mukai et al.[68] have recently reported that in an ENDOR study of the 7-*tert*-butyl-2,2,5-trimethylchromanoxyl radical the methylene hydrogens at C-4 and also those at C-3 become magnetically inequivalent at temperatures below −80 °C. This result implies that the heterocyclic ring has a nonplanar equilibrium geometry but that ringflip is rapid at room temperature.



L M

In view of the foregoing, it is surprising to find that at, and below, room temperature the radical from Ia shows hfs by only one of the pair of hydrogens at C-2 (see Table III and Figure 3).[69] Despite this, all other hfs for the Ia derived radical are very similar to those of the Ib derived radical (see Table III), and at −15 °C we even managed to achieve a partial resolution of the pair of hydrogens at C-3 (see Figure 3). At room temperature the EPR spectrum shows some changes (see Figure 3), and these may be associated with some slight motion of the heterocyclic ring. However, the change in the spectrum is not large and there is no sign that the two hydrogens at C-2 are becoming equivalent. The heterocyclic ring of the Ia derived radical must therefore be conformationally locked on the EPR time scale with a pseudoaxial H-2 ($a^H(H_{ax})$ = 3.30 G) and a pseudo-equatorial H-2 ($a^H(H_{eq})$ < 0.25 G).[70] Since the two hydrogens in position 4 of the radical derived from Ia are magnetically equivalent, we conclude that *in solution* this radical adopts a conformation somewhere between the half-chair seen in the crystal structure of Ib and Ic and a type of envelope in which the *def* angle is somewhat reduced with respect to its value in the crystal while the *fab* angle (and hence θ) may be somewhat increased. From the general similarity of the H hfs in our chromanoxyl radicals (Table III) we assume that α-tocopheroxyl and all structurally related radicals adopt generally similar conformations. We tentatively suggest two possible explanations of the difference between our EPR result for the Ia derived radical and Mukai et al.'s[68] ENDOR result on their 2,2-dimethyl-substituted chromanoxyl. One possibility is that there is a localized torsion in the heterocyclic ring by which C-3 oscillates between the position shown in structure L and a position above the aromatic plane, while C-2 remains above this plane. Such a motion would allow the two hydrogens on C-4 to become magnetically equivalent while those at C-2 remained inequivalent. An alternative possibility is that there is somewhat greater ring puckering in Ia than in Mukai et al.'s radical. This would arise because of the smaller steric interaction between 4-H_{ax} and 2-R_{ax} when R = H compared with R = CH_3, vide supra and structure G.

The reduced reactivity toward peroxyl radicals of α-T, Ia, Ic–f, and Ii and Ij relative to Ib is due to impaired ability of the 2p-type

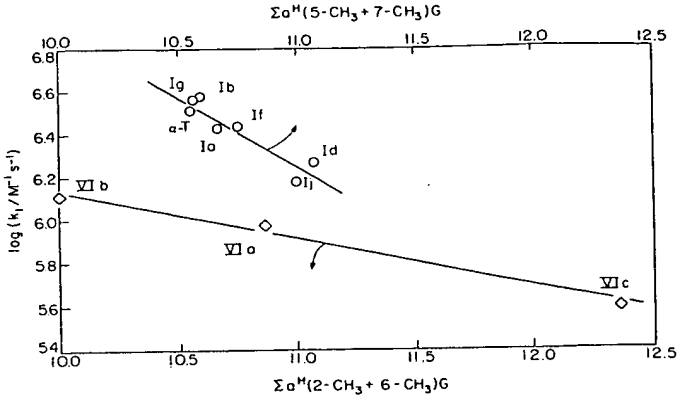


Figure 4. Plot of log (k_1/M^{-1} s^{-1}) (from Table I) vs. the sum of the hydrogen hfs by the two *o*-methyl groups in the corresponding radical (from Table III). Phenols of class I (○). Phenols of class VI (◇). For the meaning of identifying symbols, see Table I.

lone pair on the ring oxygen to participate in the delocalization of the unpaired electron and hence in stabilization of the phenoxyl radical. As discussed above, this impairment may be due to conformational effects in the heterocyclic ring (probably the situation insofar as α-T and Ia (and also, possibly Ij, vide supra) are concerned) or to polar factors (probably the principal cause of the reduced activity Ic–f and Ii–Ij, though H bonding may also play a role in Ic and Ie). Whatever the origin of the reduced stabilization of the phenoxyl there should be an increase in the spin density in the aromatic ring and this should be reflected in the hfs of the 5-CH_3 and 7-CH_3 groups. For the radicals derived from class I phenols there is, in fact, a rough correlation between log (k_1/M^{-1} s^{-1}) and $\sum a^H$(5-CH_3 + 7-CH_3), see Figure 4. A similar correlation between log (k_1/M^{-1} s^{-1}) and $\sum a^H$(2-CH_3 + 6-CH_3) exists for the 4-methoxy-2,6-dimethylphenoxyl radicals (see also Figure 4). Thus, within the classes considered in the present work the better antioxidants yield more stabilized phenoxyl radicals and these, naturally, have lower spin densities in their aromatic rings.

Decay of Phenoxyl Radicals. Lack of Effect of Oxygen. α-Tocopherol and related phenols are highly effective antioxidants because they react exceptionally rapidly with peroxyl radicals *and* because the ArO· "wasting" reactions 9, 10, 11, and 12 are relatively slow.[71]

$$\text{ArO}\cdot + \text{RH} \xrightarrow{\text{slow}} \text{ArOH} + \text{R}\cdot \qquad (11)$$

$$\text{ArO}\cdot + \text{ROOH} \xrightarrow{\text{slow}} \text{ArOH} + \text{ROO}\cdot \qquad (12)$$

The bimolecular self-reaction of α-tocopheroxyl is very slow for a radical–radical reaction, but it should be noted that our value of $2k_9$ for this radical (Table IV) is considerably larger than previously reported values.[72-74] This is due to the fact that the kinetics of decay of many ArO· radicals are complicated by the reversible formation of diamagnetic dimer and/or disproportionation products.[1c,75-78] Our own experiments were carried out

(68) Mukai, K.; Tsuzuki, N.; Ishizu, K.; Ouchi, S.; Fukuzawa, K. *Chem. Phys. Lipids* **1984**, *35*, 199–208.

(69) Note that V and probably IVc also show hfs by only one H at the 2-position.

(70) The magnitude of $a^H(H_{ax})$ and $a^H(H_{eq})$ for the H atoms attached to C-2 will depend on the spin density at the 1-oxygen atom and on the dihedral angle between this oxygen's 2p-type lone pair and the C_2–H bond in question. With certain assumptions, we estimate that the maximum probable value for $a^{H_{ax}}$ would be ca. 4 G.

(71) Although reaction 11 can occur with α-tocopheroxyl (see: Peers, K. E.; Coxon, D. T.; Chan, H. W.-S. *J. Sci. Food Agric.* **1981**, *32*, 898–904. Peers, K. E.; Coxon, D. T. *Chem. Phys. Lipids* **1983**, *32*, 49–56. Coxon, D. T.; Peers, K. E.; Rigby, N. M. *J. Chem. Soc., Chem. Commun.* **1984**, 67–68) there is no evidence that it is fast; reaction 12 must also be slow because with α-tocopheroxyl it will be endothermic by ca. 8 kcal/mol.

(72) Repges and Sernetz (Repges, R.; Sernetz, M. *Ber. Bunsenges. Phys. Chem.* **1969**, *73*, 264–267) give 180 M^{-1} s^{-1} in $CHCl_3$.

(73) Simic (Simic, M. G. In "Autoxidation in Food and Biological Systems"; Simic, M. G.; Karel, M., Eds.; Plenum Press: New York, 1980; pp 17–26) gives 350 M^{-1} s^{-1} in cyclohexane.

(74) Tsuchiya et al. (Tsuchiya, J.; Niki, E.; Kamiya, Y. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 229–232) give 0.061 M^{-1} s^{-1} in benzene.

(75) Weiner, S. A. *J. Am. Chem. Soc.* **1972**, *94*, 581–584.

(76) Mahoney, L. R.; Weiner, S. A. *J. Am. Chem. Soc.* **1972**, *94*, 585–590.

(77) Weiner, S. A.; Mahoney, L. R. *J. Am. Chem. Soc.* **1972**, *94*, 5029–5033.

with "fresh" α-tocopheroxyl, and decay followed clean second-order kinetics for 80% or more of the reaction.

With the exception of the radical derived from V, the rate constants for phenoxyl radical decay in oxygen-saturated (760 torr) solutions were not significantly different from the values obtained under oxygen-free conditions (see Table IV), which indicates that $k_{10} \ll 2k_9[\mathrm{ArO}\cdot]/[\mathrm{O_2}]$. Under these conditions the oxygen concentration is ca. 9.2×10^{-3} M.[28] In a typical experiment the initial α-tocopheroxyl radical concentration was ca. 2×10^{-5} M and, hence, k_{10} must be $\ll 6.5\ \mathrm{M^{-1}\ s^{-1}}$ for this radical. The $C_6H_5O\cdot$ radical has also been shown to be unreactive toward oxygen on the time scale of its bimolecular self-reaction,[28] which is, however, diffusion controlled.[79] The 2,4,6-tri-*tert*-butylphenoxyl/O_2 reaction appears to be the only other phenoxyl/oxygen reaction to have been investigated kinetically.[80] Decay follows termolecular kinetics,[80] and k_{13} can be calculated to be ca. $3 \times 10^5\ \mathrm{M^{-2}\ s^{-1}}$ at 25 °C. If α-tocopheroxyl reacts with oxygen in a similar manner then $k_{13} \ll 2k_9[\mathrm{ArO}\cdot]^2/[\mathrm{ArO}\cdot]^2[\mathrm{O_2}] = 3 \times$

$$2\mathrm{ArO}\cdot + \mathrm{O_2} \rightarrow \text{nonradical products} \qquad (13)$$

$10^5\ \mathrm{M^{-2}\ s^{-1}}$. That is, α-tocopheroxyl is even less reactive toward oxygen than is tri-*tert*-butylphenoxyl. We conclude that the slowness of the reaction between α-tocopheroxyl and oxygen is yet one more reason why α-T appears to have been selected as nature's major lipid-soluble, chain-breading antioxidant.[1b]

Experimental Section

Materials. Commericial samples of **(*R*,*R*,*R*)-α-tocopherol** (α-T; Eastman), **(*R*,*R*,*R*)-γ-tocopherol** (γ-T; Eastman), ***rac*-5,7-dimethyltocol** (DMT; Supelco), **2,3,4,6-tetramethylphenol** (VIe; Aldrich), **2,6-dimethylphenol** (VIh; Aldrich), **2,6-di-*tert*-butyl-4-methylphenol** (VIIb; Aldrich), and **2,6-di-*tert*-butylphenol** (VIIc, Eastman) were used without further purification. **2,4,6-Trimethylphenol** (VIf) was a sample of recrystallized material used in previous studies.

(*R*,*R*,*R*)-β-Tocopherol (β-T), **(*R*,*R*,*R*)-δ-tocopherol** (δ-T), **6-hydroxy-2,2,5,7,8-pentamethylchroman** (Ib), **2,3,5,6-tetramethyl-4-methoxyphenol** (VIc), **pentamethylphenol** (VId), **2,3,5,6-tetramethylphenol** (VIg), and **2,6-di-*tert*-butyl-4-methoxyphenol** (VIIa) were obtained as described previously.[3b] **6-Hydroxy-5,7,8-trimethylchroman** (Ia), **2,3-dihydro-5-hydroxy-2,4,6,7-tetramethylbenzofuran** (IIIa), and **2,3-dihydro-5-hydroxy-2,2,6,7-tetramethylbenzofuran** (IIId) were gifts from Drs. F. M. Dean and L. H. Sutcliffe (University of Liverpool, Liverpool, England). Ia and IIId were used as received. ^{1}H NMR and thin-layer chromatography of a sample of IIIa revealed the presence of a small amount of an impurity. Gas chromatography–mass spectrometry of the trimethylsilyl ethers indicated that the impurity represented about 5% of the mixture and was 2 mass units less than IIIa. The sample was purified by "flash" chromatography on silica gel[81] with 8% ethyl acetate in hexane (v/v). The impurity was tested by the inhibited-autoxidation method and was found to possess only weak antioxidant properties. **6-Hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid** (Ic), **methyl 6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxylate** (Id), **6-hydroxy-2,5,7,8-tetramethylchroman-2-acetic acid** (Ie), **6-hydroxy-2,5,7,8-tetramethylchroman-2-propionic acid** (Ig), **6-hydroxy-2-(hydroxymethyl)-2,5,7,8-tetramethylchroman** (Ii), **6-hydroxy-2,5,7,8-tetramethyl-2*H*-chromen-2-acetic acid** (IIb), and **2,3-dihydro-5-hydroxy-2,4,6,7-tetramethylbenzofuran-2-carboxylic acid** (IIIc) were gifts from Dr. J. W. Scott (Hoffman-LaRoche, Nutley, NJ) and were used as received.

Unless otherwise noted, in the synthetic procedures described below reactions were carried out under an atmosphere of argon and solvents were dried by refluxing over CaH_2 followed by fractional distillation under argon. Column chromatography was performed by the "flash" method[81] with Merck silica gel grade 60, 230–400 mesh. The progress of a reaction was usually monitored by thin-layer chromatography (TLC) with BDH (Merck) silica gel 60 F-254 plates. These plates were generally developed with use of a 12% ethyl acetate:*n*-hexane (v/v) solution and spots were visualized with use of a phosphomolybdic acid spray (3.5%, Merck) followed by heating. Melting points were determined on a Fisher Digital Melting Point Apparatus and are uncorrected. ^{1}H NMR spectra were generally measured on a Varian EM-360A spectrometer, and chemical shifts are reported relative to Me_4Si as an internal standard. Mass spectra were measured on a Hewlett Packard 5995 GC/MS with a 10 m × 0.2 mm i.d., Ultra 1 (OV-101) column.

The methyl esters, **methyl 6-hydroxy-2,5,7,8-tetramethylchroman-2-acetate** (If) and **methyl 6-hydroxy-2,5,7,8-tetramethylchroman-2-propionate** (Ih), were synthesized from the parent acids, Ie and Ig, following a published procedure.[82] If was obtained as a waxy solid (mp 59.2–60.0 °C) which could not be recrystallized, and Ih was obtained as white crystals after recrystallization from hexane/methylene chloride (mp 107.5–108.5 °C). Both compounds showed only one spot on TLC. Compounds prepared by published methods were **6-hydroxy-2-methoxy-2,5,7,8-tetramethylchroman** (Ij),[83] **4-methoxy-2,6-dimethylphenol** (VIa),[84] and **4-methoxytrimethylphenol** (VIb).[84] These compounds all had melting points in satisfactory agreement with their published values.[83,84]

6-Hydroxy-2,2,5,7,8-pentamethyl-2*H*-chromene (IIa), 4.0 g of Ib (18 mmol), 8.5 mL of acetic anhydride (90 mmol), and 3.75 g of sodium acetate (40 mmol) were heated at 100 °C for 30 min. The mixture was poured into 100 g of ice water and stirred for 1 h. The precipitate was filtered, washed with water, and dried under high vaccum for 12 h to yield 4.8 g of **6-acetoxy-2,2,5,7,8-pentamethylchroman** (Ik; 100%). Ik was converted into **6-acetoxy-2,2,5,7,8-pentamethyl-2*H*-chromene** (IIc) following the published procedure[85] for synthesizing 3,4-dehydro-α-tocopherol from α-T. 2,3-Dichloro-5,6-dicyanobenzoquinone (4.83 g, 21.2 mmol) was added in portions over 4 h to 4.8 g of Ik (18 mmol) in 120 mL of toluene at 120 °C under an atmosphere of nitrogen. The reaction was maintained at this temperature for 12 h after addition was complete. The mixture was cooled to 5 °C and filtered. The filtrate was evaporated and the residue subjected to "flash" chromatography[81] on silica gel with 5% ethyl acetate in hexane (v/v) as eluent. IIc was obtained as an oil which crystallized on standing (2.37 g; 49%). IIc (1.34 g, 5 mmol) in 13 mL of diethyl ether was added dropwise to a stirred suspension of 0.88 g of lithium aluminum hydride (23 mmol) in 13 mL of diethyl ether at room temperature. The mixture was stirred for 30 min. Moist ether was added to decompose the catalyst, followed by 18 mL of 1 N sulfuric acid. The reaction product was extracted into ether and the ether layer washed successively with water, sodium bicarbonate solution, and finally water. The ether extract was dried over sodium sulfate and evaporated to give 0.6 g of IIa (54% after one recrystallization from *n*-hexane, mp 70.3–71.8 °C): ^{1}H NMR ($CDCl_3$) δ 1.40 (s, 6, alkyl CH_3), 2.20 (s, 9, aromatic CH_3), 4.25 (s, 1, OH), 5.52 (d, J = 10 Hz, 1, vinyl H), 6.40 (d, J = 10 Hz, 1, vinyl H), Anal. Calcd for $C_{14}H_{18}O_2$: C, 77.02; H, 8.31. Found: C, 76.85; H, 8.13.

2,3-Dihydro-5-hydroxy-2,2,4,6,7-pentamethylbenzofuran (IIIb) was prepared by following the published procedure for the synthesis of IIId.[86] Trimethylhydroquinone (Aldrich; 0.1 mol) and 2-methyl-2-propen-1-ol (Aldrich; 0.1 mol) were refluxed for 48 h in anhydrous formic acid (400 mL, prepared by heating for 2 h with an excess of phthalic anhydride, followed by fractional distillation) containing 20 drops of concentrated sulfuric acid. The reaction mixture was poured on ice and extracted with ether (2 × 300 mL). The ether extract was washed with water (2 × 300 mL), aqueous sodium bicarbonate (2 × 300 mL), and saturated aqueous sodium chloride (300 mL) and dried over sodium sulfate. The residue obtained after evaporation of the ether was refluxed for 15 min in methanol (300 mL) containing concentrated hydrochloric acid (3 mL). The cooled reaction mixture was treated with methylene chloride (500 mL) and filtered to remove unreacted trimethylhydroquinone. The filtrate was washed with aqueous sodium bicarbonate (100 mL), water (100 mL), and saturated aqueous sodium chloride (100 mL) and dried over sodium sulfate. The residue obtained after evaporation was purified by flash chromatography on silica gel with 3% ethyl acetate in *n*-hexane and finally recrystallized from aqueous methanol to give fluffy, white crystals (2.5 g; 12% yield): mp 122–123 °C; ^{1}H NMR ($CDCl_3$) δ 1.47 (s, 6 H, alkyl CH_3), 2.15 (s, 9 H, aromatic CH_3), 2.87 (s, 2 H, CH_2), 4.15 (s, 1 H, OH). The NMR assignments agree well with the published data for IIId.[86] GC–MS of the trimethylsilyl ether gave the correct parent ion at 278 daltons. Anal. Calcd for $C_{13}H_{18}O_2$: C, 75.69; H, 8.79. Found: C, 75.86; H, 8.85.

1,2,3,4-Tetrahydro-6-hydroxy-5,7,8-trimethylquinoline (IVa) was prepared by modifying an earlier, published procedure.[87] Trifluoroacetic

(78) α-Tocopheroxyl has, in fact, been reported to dimerize at low temperatures.[60]

(79) Dobson, G.; Grossweiner, L. I. *Trans. Faraday Soc.* **1965**, *61*, 708–714.

(80) Griva, A. P.; Denisov, E. T. *Int. J. Chem. Kinet.* **1973**, *5*, 869–877.

(81) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923–2925.

(82) Cohen, N.; Banner, B. L.; Neukom, C. *Synth. Commun.* **1982**, *12*, 57–65.

(83) Scott, J. W.; Bizzarro, F. T.; Parrish, D. R.; Saucy, G. *Helv. Chim. Acta* **1976**, *59*, 290–305.

(84) John, W.; Rathmann, F. H. *Chem. Ber.* **1940**, *73*, 995–1001.

(85) Mayer, H.; Isler, O. In "Methods in Enzymology"; McCormick, D. B.; Wright, L. D., Eds.; Academic Press: New York, 1971; Vol. 18, Part C, pp 241–348.

(86) Lars, J.; Nilsson, G.; Selander, H.; Sievertsson, H.; Skånberg, I. *Tetrahedron* **1970**, *26*, 879–886.

acid (3.8 mL, 50 mmol) was added to a suspension of 10 g of 6-hydroxy-5,7,8-trimethylquinoline[87] (53 mmol) in 200 mL of methanol. The resulting solution was hydrogenated at 40 psi for 2.5 h in the presence of platinum oxide (1 g). After this time, the mixture was filtered through Celite and the filtrate evaporated to yield 13.9 g of 6-hydroxy-5,7,8-trimethylquinolinium trifluoroacetate (87%; mp >300 °C). The quinolinium trifluoroacetate salt (7 g) was suspended in 140 mL of 95% ethanol and 35 mL of a saturated sodium bicarbonate solution was added, followed by 140 mL of water. After partial evaporation and cooling of the solution a precipitate formed which was filtered off and dried under high vacuum for 12 h to give 4.1 g of IVa (93%). Recrystallization from ethyl acetate gave pale brown crystals, mp 132.7–132.9 °C (lit.[87] mp 128–131 °C), which turned darker brown over a period of days.

1-Acetyl-1,2,3,4-tetrahydro-6-hydroxy-5,7,8-trimethylquinoline (IVb) was prepared from IVa by the method reported in the literature.[87]

1-Ethyl-1,2,3,4-tetrahydro-6-hydroxy-5,7,8-trimethylquinoline (IVc). A solution of 4.1 g of IVb (20 mmol) in 20 mL of dry tetrahydrofuran was added dropwise to a suspension of 1.6 g of lithium aluminum hydride (42 mmol) in 20 mL of the same solvent, while maintaining a gentle reflux. The mixture was refluxed for a further hour after the addition was complete. The reaction mixture was then cooled in ice and 50 mL of a solution of ethyl acetate in tetrahydrofuran (1:1 (v/v)) was slowly added dropwise. This was followed by the addition of 50 mL of ethyl acetate and finally 150 mL of 3 M HCl. The milky suspension was separated and a saturated solution of sodium bicarbonate was added slowly, with stirring and cooling at 5 °C, to the aqueous fraction. The suspension was then extracted with ethyl acetate (2 × 250 mL) and the ethyl acetate extract washed with saturated sodium chloride solution (1 × 50 mL) and dried over sodium sulfate. Evaporation of the ethyl acetate gave a white precipitate which was recrsytallized from hot *n*-heptane and ethyl acetate to give 1.0 g of IVc (25%; mp 141.4–141.6 °C): ^{1}H NMR ($(CD_3)_2SO$) δ 1.15 (t, J = 7 Hz, 3, ethyl CH_3), 1.5–1.8 (m, 2, ring CH_2), 1.90 (s, 3, aromatic CH_3), 2.10 (s, 6, aromatic CH_3), 2.45 (m, 4, ring CH_2 and *N*-ethyl CH_2), 2.7–3.0 (m, 2, benzylic CH_2). Anal. Calcd for $C_{14}H_2NO$: C, 76.66; H, 9.65; N, 6.38. Found: C, 76.49; H, 9.57; N, 6.44.

3,4-Dihydro-6-hydroxy-4,4,5,7,8-pentamethyl-2*H*-1-(benzothio)pyran (V). 4-Mercaptotrimethylphenol[42] (1.1 g, 6.5 mmol), 12 mL of anhydrous formic acid, and 1.0 mL of 3-methyl-2-buten-1-ol (9.8 mmol) were refluxed under argon for 2 h. The reaction mixture was cooled to 5 °C, diluted with 20 mL of water, and extracted with ether (3 × 25 mL) and the combined ether layer washed with cold 1 M sodium hydroxide solution. The separated ether fraction was dried over sodium sulfate and the ether was removed by evaporation. The brown oil obtained was gently refluxed for 1 h with 12 mL of 6% methanolic potassium hydroxide under argon. The cooled solution was diluted with 20 mL of water and extracted with ether (3 × 25 mL). The combined ether extracts were washed with water (2 × 15 mL) and dried over sodium sulfate and the ether removed to give 0.9 g of a brown resin. This residue was subjected to careful medium-pressure chromatography on silica gel with 5% ethyl acetate in hexane (v/v). A yellow oil was obtained as the main fraction (0.52 g) which, after trituration with *n*-hexane and standing overnight at 0 °C, yielded 0.1 g of colorless crystals of V. The remaining yellow oil resisted all attempts at further crystallization. The crystalline material was recrystallized from *n*-hexane (mp 86.4–87.3 °C). ^{1}H NMR (at 80 MHz in $CDCl_3$) δ 1.45 (s, 6, $C(CH_3)_2$), 1.87–2.13 (m, 2, CH_2), 2.13 (s, 3, aromatic CH_3), 2.25 (s, 3, aromatic CH_3), 2.42 (s, 3, aromatic CH_3), 2.75–3.00 (m, 2, CH_2), 4.50 (s, 1, OH). Anal. Calcd for $C_{14}H_{20}OS$: C, 71.14; H, 8.53. Found: C, 70.49; H, 8.66. X-ray diffraction analysis confirmed the assigned structure.

Measurement of k_1 Values by the IAS Method. Oxygen uptake was monitored essentially as described before[3b] with a more sensitive pressure transducer (Validyne, Northridge, Calif.; 65 torr full-scale) with use of (a) 25 mM AIBN in 7.0 mL of vacuum-distilled styrene and 1.0 mL of chlorobenzene for the more reactive antioxidants or (b) 20 mM AIBN in 1 mL of styrene and 1 mL of chlorobenzene for the less reactive compounds. The k_1 values were determined from the averaged product of the slope, $d[O_2]/dt$, and the projected, remaining induction period, τ, at several points on the inhibited oxidation curve (for inhibited rates less than 10% of the final, uninhibited rate) by using the fact that $(d[O_2]/dt)\tau = k_2[\text{styrene}]/k_1 = \text{a constant}$. The k_1 value relative to α-tocopherol was obtained directly by taking the ratio of the $((d[O_2]/dt)\tau)$ product. Absolute values of k_1 could then be calculated by using the k_1 value for α-tocopherol (determined many times) or by using the calibration factor for the apparatus (and reaction flask) together with the known value for k_2 and the concentration of styrene.

Measurement of k_1 Values by the LKEPR Method. Small quantities of the phenol were dissolved in a mixture of di-*tert*-butyl ketone (0.90 M) and cyclopentane or *n*-decane and the solution was saturated with O_2 at 760 torr by bubbling for 10–20 min. The phenol concentration was in the range 2×10^{-5} to 6×10^{-4} M depending upon its reactivity. For all of the more reactive phenols a flow system was employed. These solutions were subjected to the pulse from a nitrogen laser (337 nm, ~8 ns, up to 10 mJ/pulse) while flowing through the cavity of a Varian E 104 EPR spectrometer at a temperature of 24 °C. Since the highly reactive phenols were used at rather low concentrations, it was necessary to replace the portion of the sample photolyzed by fresh solution after each light pulse in order to prevent excessive depletion of the phenol. The decay of the EPR signal due to the $Me_3COO\cdot$ and $Me_3CC(O)OO\cdot$ radicals was monitored at a fixed magnetic field. Interference with the peroxyl decay trace from the "grow-in" of the phenoxyl signal was avoided by working on the low-field tail of the peroxyl signal (3215 G at 9.13 GHz) under conditions of high modulation amplitude (8 G) and high microwave power (100 mw).[88] Up to 140 individual decay traces were collected and averaged on a Nicolet 1170 signal averager. Values of k_1 were calculated as described in the Results Section.

X-ray diffraction. These studies were performed with an automatic 4-circle Picker diffractometer by the $\theta/2\theta$ scan method with line profile analysis.[89] The cell parameters were obtained by least-squares refinement of the setting angles of reflections with large 2θ values. Structures were determined for compounds Ic, IIb, IIId, and V. Compound Ic was recrystallized from hexane–methylene chloride, compound IIb from aqueous ethanol, and compound V from hexane, and compound IIId was used as received. The structures were solved with the direct methods program MULTAN[90] and refined by block diagonal least squares with counting statistics weights. Scattering curves for neutral atoms were taken from the literature,[91] and an extinction correction[92] was included in the calculations which were performed with use of the NRC PDP8-E system of programs.[93] Details of space group, unit cell, data collection, and residuals are given in Table VI of the Supplementary Material.

EPR Spectra. Solutions of the phenols (ca. 5×10^{-2} M) in benzene/di-*tert*-butyl peroxide (5:1 (v/v)) were degassed and sealed under vacuum in quartz EPR cells. Phenoxyl radicals were generated by continuous low-intensity UV irradiation of the sample tube in the cavity of a Varian E104 EPR spectrometer at room temperature. The spectrum of the radical derived from **Ia** was obtained in the same general way, the precise experimental conditions being described in the caption to Figure 3. EPR parameters were determined with the aid of a Varian NMR Gauss meter and a microwave frequency meter (Autohet Counter Model 350 D) with use of the tetracene radical cation (g = 2.002 604) as a reference for the g values and comparison with computer-simulated spectra for the hyperfine splittings.

Phenoxyl Radical Decay Kinetics. Phenoxyl radicals were generated essentially instantaneously by a brief flash of intense UV irradiation of a sample containing ca. 5×10^{-2} M phenol in benzene/di-*tert*-butyl peroxide (10:1 (v/v)). These solutions either were sealed under vacuum or were continuously saturated with oxygen at a pressure of 760 torr. Decay of the phenoxyl radicals was monitored at a fixed magnetic field which was preset to the main peak in the phenoxyl spectrum. Phenoxyl radical concentrations were determined by comparison with a standard solution of diphenylpicrylhydrazyl in the usual way.[94]

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Registry No. Ia, 21704-70-1; Ib, 950-99-2; Ic, 56305-04-5; Id, 86646-83-5; Ie, 86646-84-6; If, 98760-49-7; Ig, 4072-32-6; Ih, 98760-50-0; Ii, 79907-49-6; Ij, 98777-24-3; Ik, 57721-81-0; IIa, 56306-89-9; IIb,

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Supplementary Material Available: Tables VI–XXI giving detailed X-ray crystallographic data, final parameters, and structural factor lists (70 pages). Ordering information is given on any current masthead page.

The Formation of an Enantiomerically Pure Product of Free Radical Coupling. The Chemistry of Diphenylcarbene in Polycrystalline (*S*)-(+)-2-Butanol[1]

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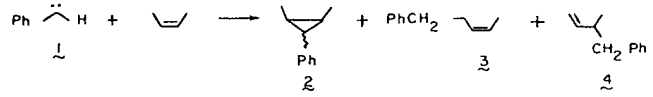
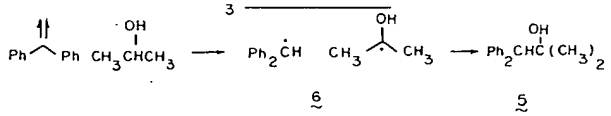
Abstract: Photolysis of 0.1 M diphenyldiazomethane at 77 K or 137 K in solid (*S*)-(+)-2-butanol gives tertiary alcohol **9** along with other products. Compound **9** was isolated and found to be enantiomerically pure by chiral NMR shift reagents. Compound **9** is formed by reaction of triplet diphenylcarbene with (*S*)-(+)-2-butanol to give a radical pair which subsequently collapses. The solid-state matrix directs the radical pair collapse with complete retention of configuration.

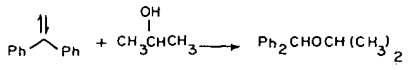
In 1971 Moss and Dolling discovered that the photochemical generation of arylcarbenes in low-temperature solids enhances the yield of triplet-derived products.[3] Phenylcarbene **1** reacts with *cis*-2-butene in solution to give >85% of cyclopropanes **2** (syn and anti) and only a small (<15%) amount of olefins **3** and **4**. In the solid state (−196 °C) the yield of **3** plus **4** exceeds 50% and the yield of **2** drops below 50%.



In subsequent years several more examples of the unusual solid-state chemistry of arylcarbenes have been reported by Moss,[4] Tomioka,[5] and Platz.[6] Tomioka discovered that diphenylcarbene (DPC) reacts with 2-propanol in the solid state to give high yields of alcohol **5**, presumably by hydrogen atom abstraction by triplet DPC to give radical pair **6**. In solution phase only trace amounts



of **5** are formed, the near exclusive product being ether **7** derived from reaction of singlet DPC with solvent. It occurred to us that



if a chiral alcohol were employed as a polycrystalline matrix then a radical pair (such as **6**) would again be formed. The rigid polycrystalline environment should prevent rotational motion of the components of the radical pair and direct their collapse to form a stable product in only one sense to give an enantiomerically enriched material. As described in the next section these expectations were confirmed in the diphenylcarbene–2-butanol system.

Table I. Absolute Yield (±2%) of Products Formed by the Reaction of DPC with D,L-2-Butanol and (*S*)-(+)-2-Butanol at 77 K

	absolute yield (%)	
product	D,L-2-butanol	(*S*)-(+)-2-butanol
8	6	6
9	12	13
10	5	6
11	1	1
12	1	1
13	11	10
total	36	37

Table II. Absolute Rate of Decay of Triplet DPC in D,L- and (*S*)-(+)-2-Butanol at 98 K (Three Trials Each)

D,L k ($s^{-1/2}$)	(*S*)-(+) k ($s^{-1/2}$)
2.96×10^{-2}	2.69×10^{-2}
2.73×10^{-2}	2.50×10^{-2}
2.60×10^{-2}	2.80×10^{-2}
av $2.8 \pm 0.2 \times 10^{-2}$	av $2.7 \pm 0.2 \times 10^{-2}$

Results

The DPC–2-butanol system was chosen based upon Tomioka's results and the accessibility of enantiomerically pure (*S*)-(+)-2-

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